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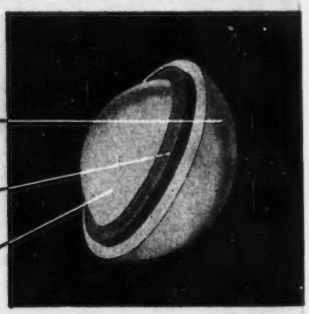

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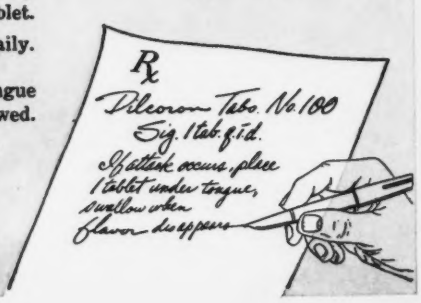

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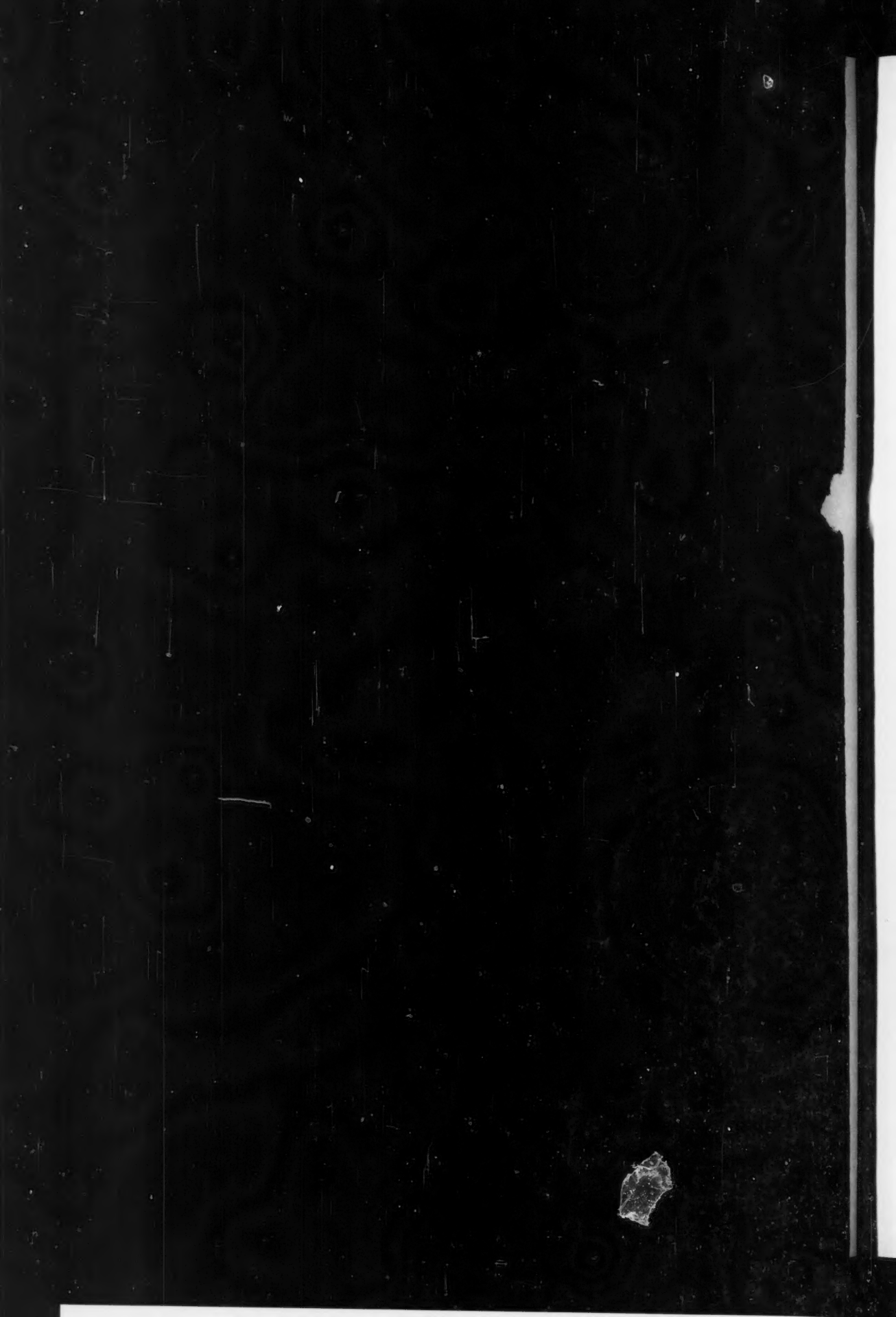

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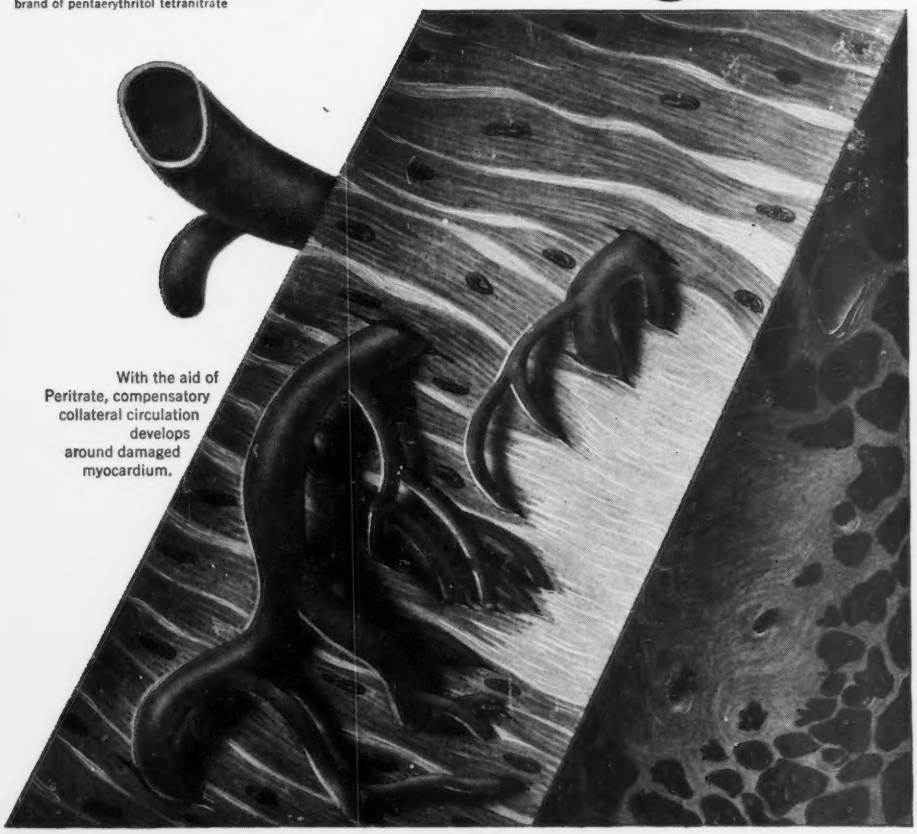

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Editorial

Atherosclerosis, Infarction, and Nutrition

DIETARY factors are now generally considered to play a causative role in myocardial, cerebral, renal, aortic, and peripheral atherosclerosis. This view is based on the cholesterol-lipid-lipoprotein concept of atherosclerosis. Central to this formulation is that fat intake over the life span is a major factor influencing human atherogenesis. At a time when the physician is pressured to do something about the high incidence of coronary and cerebral artery disease, it is important to reexamine frequently the soundness of this theory and to assess whether it warrants practical recommendations regarding therapy and prophylaxis.

Of the many factors related to the problem of atherosclerosis, it appears easier to change individual nutrition than heredity and certainly less desirable than attenuating one's sex. Nutritional theory, however, is not merely the offspring of a *Zeitgeist,* but is the result of an imposing array of clinical epidemiologic and experimental observations. First of all, atherosclerotic lesions have a high cholesterol and lipid content. Secondly, lesions in animals are invariably achieved by any dietary modification that results in a sustained elevation of serum cholesterol. Thirdly, an increase of atherosclerosis occurs in man when lipid and carbohydrate metabolisms are abnormal. Finally, wide-ranging epidemiologic studies reveal that atherosclerosis is associated with the composition, including the fat content, of the diet.

The Lesion. Virchow's demonstration of the fatty nature of the atheromatous lesion provided circumstantial evidence for the lipid hypothesis. It has since been shown that with increasing severity of the atheromatous process there is a greater concentration of total extractable lipids, cholesterol, and fatty acids in the involved areas of aorta. This is probably not the result of a nonselective infiltration and precipitation. No quantitative relationship is demonstrable between concentration in serum and aorta of total extractable lipids and cholesterol in human subjects of varying ages. Such a correlation is found in xanthomatosis in association with high cholesterol levels, and in the early lesions of experimentally induced atherosclerosis.

The vascular compartment is not only a conduit but a metabolizing tissue. The healthy, and diseased, arterial wall can synthesize cholesterol, fatty acids, and phospholipids. Thus, the concentration of lipids in the atheromatous lesion may not be due solely to a systemic derangement. It may be the result of a local process either of overproduction or reduced outward transport. This line of evidence, therefore, does not necessarily settle the question of whether cholesterol plays a primary or secondary role in the production of intimal plaques.

Experimental Atherosclerosis. Major support for the nutritional hypothesis is provided by the production of atherosclerosis in ani-

From the Department of Nutrition, Harvard University School of Public Health, and the Medical Service, Peter Bent Brigham Hospital, Boston, Mass.

mals. Most experimental lesions, resembling human atherosclerosis, have been produced by dietary manipulation that includes the addition of cholesterol to the diet. Incorporation of 1 mg. of cholesterol per 3 to 5 calories of food will result in a marked hypercholesteremia and subsequent atherosclerosis. The greater the amount of dietary cholesterol, the shorter is the interval for achieving an elevated blood cholesterol level and subsequent significant atheromatous lesions. Marked species differences exist in susceptibility to atherosclerosis induced by diet. It is difficult to produce such lesions in rats unless small amounts of bile acids are also fed. In dogs they are difficult to produce unless the thyroid gland is blocked in addition. In monkeys the use of a sulfur-deficient protein, as well as cholesterol and bile acids, accelerates their development. Variations in any of the major components of the diet, fat, protein, and carbohydrate, may affect the serum cholesterol level and predispose to atherosclerosis. Thus diets high in fats, particularly those providing much oleic acid, favor the development of atherosclerosis as compared with those low in fat or those providing more linoleic acid. In the rat, diets low or high in protein are more atherogenic than those with moderate amounts, and starch as the main source of carbohydrate gives lower levels of serum cholesterol than sucrose.

Other nutrients may also be involved. For example, on an atherogenic diet low in magnesium a growing rat develops more severe atherosclerosis than one on a diet identical except for the increase of this mineral. Conversely, when dietary magnesium concentration is high, the lesions are reduced.

Considerable caution is necessary in transferring these observations from experimentally induced atherosclerosis to the human disease. The experimental animal and spontaneous human lesions show differences in morphology and distribution. For example, in the cholesterol-lipid feeding experiments in the species commonly used (the rabbit, chick, monkey, and rat), involvement of the aorta is generally seen in the ascending portion and arch, in contrast to the preponderant abdominal involvement of the full-blown human disease. In most of the experimental reports, involvement of the valvular endocardium and the pulmonary arteries has been distinctly more marked than in human atherosclerosis. Gross involvement of the cerebral arteries has been seen only in the Rhesus monkey and then in the absence of any of the central nervous system lesions associated with the human disease. Concomitant pathology of the smaller arteries and arterioles, frequent in man with such serious sequelae as retinitis and renal dysfunction, has not been seen in the experimental animal.

Among the different experimental species there is a considerable spectrum in the extent of extravascular lipid deposition (liver, adrenal glands, and reticuloendothelial system), being perhaps most prominent in the rabbit and least so in the monkey. Such lipid deposition is not a component of human atherosclerosis, nor is the cirrhosis seen in the fatty livers of rabbits and rats with far-advanced arterial lesions. Finally, at a microscopic level, there are various differences between the experimental and the human lesions. These include the prominence of foam-cell accumulations, the degree of medial involvement, the amount of collagenous stromal reaction, the presence of hemorrhage, the deposition of calcium, and the presence of thrombotic and ulcerative phenomena involving the endothelium. Perhaps the most important difference between animal and human atherosclerosis is that coronary thrombosis and myocardial infarction are not usual end results of atheromatosis in the experimental animal. An exception has been reported recently in rat experimentation, but this involved the imposition of multiple severe dietary abnormalities as well as thyroid ablation.[1] This interesting observation needs further confirmation.

In this context the following 2 observations may be relevant. Animals in captivity are reported to show an increasing incidence of atherosclerosis. So far, this has not been re-

ated either to diet or age. "Social pressure" nd captivity have been implicated as respon- ible factors. Administration of catechols may nhance or, in proper settings, evoke vascular esions, again achieved without dietary modi- ications.

In translating the meaning of animal ex- eriment to human experience several reser- ations are in order. First of all, there is a triking species variability, and animals vary greatly in susceptibility to dietary provoca- ion. Secondly, similarities in pathologic mor- phology between animal and human athero- sclerosis do not necessarily indicate that the pathogenesis of the lesion in both is the same. Thirdly, no animal experiment, however con- clusive the result, provides more than circum- stantial evidence regarding the human process. In the last analysis, man must answer the quandaries of his own biologic aberrations through self study.

Clinical Correlations. In man the most cogent evidence in favor of the nutritional hypothesis is that prolonged hyperlipemia, ir- respective of cause, is associated with prema- ture atherosclerosis. The data are of 2 types: (1) the well established high incidence of atherosclerosis in certain diseases associated with hypercholesteremia, such as diabetes, myxedema, nephrosis, and familial hyperchol- esteremic xanthomatosis; (2) the demonstra- tion that, in any population, coronary disease is more prevalent in groups exhibiting hyper- cholesteremia.

There are discrepancies in the clinical evi- dence, raising significant reservations about the implication of these observations. While severe atheromatosis may exist in myxedema nd nephrosis, seldom are these entities com- plicated by myocardial infarction. In neither f these 2 diseases has the hyperlipemia been elated to nutritional abnormalities. In dia- etes mellitus and hypercholesteremic xan- homatosis a genetic element is operative. ven in apparently healthy persons evidence accumulating that the serum cholesterol ay be determined by a genetic component. a study of familial groups with hypercho- lesteremia, no difference in incidence of coro- nary artery disease was found among those with high serum cholesterol values as con- trasted with those with normal ones. Human pathologic studies have established no definite relationship between the level of the serum lipid fraction and the severity of the athero- sclerotic process. Administration of estrogens to patients with coronary artery disease has not resulted in amelioration of the disease process, although it is reported to affect the lipid concentration. No defect in lipid metab- olism can be uncovered by the challenge of a lipid load in patients with atherosclerosis. Neither single nor repeated fatty meals dis- tinguish the lipid pattern of the patient with coronary disease from that of the normal individual.

There are a number of factors in human life, unrelated to blood lipids, that play an atherogenic role. For example, the pulmo- nary artery, invariably spared in atheroscle- rosis, is the only vessel affected in the presence of pulmonary hypertension. The most severe systemic complications of atherosclerosis are generally seen with advanced hypertensive disease and clearly relate to the height of diastolic pressure irrespective of the levels of serum cholesterol or the concentrations of light or dense lipoproteins.

Even if one were to assume a good correla- tion between blood cholesterol and lipid levels on the one hand and the presence of athero- sclerosis on the other, this by itself would not establish causality. The lipid derangement may derive from the diseased state or both may result from the same etiologic process. Implicit in contemporary nutritional theory is that the blood derangements as well as the atherosclerotic lesions have their genesis in the dietary abnormalities of the individual, and that such derangements may be normalized by changes of the diet. In effect, many regard the fat content of the diet, both quantitative and qualitative, as the main environmental factor in the etiology of both disorders. Epi- demiologic studies provide some data on this aspect of the problem.

Epidemiologic Studies. Studies of different world populations suggest that serum cholesterol levels are highest in those populations with the most abundant fat intake. Other factors, such as dietary cholesterol, total calories, incidence of obesity, and racial background, do not appear to be as closely related to coronary artery disease. In the majority of these studies, estimation of diet was based on information concerning food stuffs available for consumption. Prevalence of disease, when it was included, was usually derived from mortality data based on death certificates. It needs to be emphasized that calculation of diets based on the relative amounts of food available for consumption does not reflect actual consumption. Furthermore, death certificates in different countries reflect discrepancies in disease definition, reporting patterns, and a host of other variables. Little autopsy information has been available for most of the epidemiologic studies.

Even when these facts are disregarded, the relation between fat intake and atherosclerosis provides some discrepancies. Apparent consumption of total fat, as well as animal fat, is similar in countries where the incidence of fatal coronary artery disease is very different. In countries with approximately the same percentage of fat in the diet, heart disease mortality ranges from 220 to 739 per 100,000. For example, in the range between 30 and 40 per cent of dietary fat there appears the entire gamut of heart disease mortality, varying from less than 300 per 100,000 for Austria to as much as 739 per 100,000 for the United States.

Epidemiologic findings have had a profound effect on medical thinking. It is therefore appropriate to cite the inherent limitations in such studies, as has been emphasized by Yerushalmy and Hilleboe.[2] The methods employed are indirect, and the primary unit of observation is the group. Such studies never provide proof of a cause and effect relationship. In epidemiologic data, one is searching for valid associations, namely, specific ones. It is always important to check whether the observed association is specific for the variables themselves or merely reflects a diffuse relationship with other factors. In the case of the relationship between atherosclerosis and dietary fats, testing the specificity of this association by epidemiologic data requires determining the relationship between the calorie content of another nutrient and heart disease as well as establishing the relationship between fat intake and the incidence of noncardiac disease. When such a test for specificity was carried out on available world data, it was shown that the association between protein consumption and heart disease was at least as strong as that for fat and heart disease; in addition, a strong negative association was found for both the intake of animal protein and fat with mortality from noncardiac disease.[2] Thus, world epidemiologic studies do not support the view that dietary fat is uniquely associated with death from heart disease, though this possibility is not ruled out.

While world-wide epidemiologic surveys do not provide evidence for a sole association between dietary fat and heart disease, these studies do indicate that when the diet is low in animal fat, there is a low incidence of coronary artery disease. But a diet low in fat is usually also deficient in animal protein and sucrose, is usually high in fiber and starch, and differs in its composition in minerals and vitamin content. Each of these factors has been shown to affect the cholesterol level in experimental studies with animals. Finally, a low animal-fat diet generally reflects a state of underdevelopment of a group or nation with a host of attendant social, cultural, and medical differences, all of which may exert an influence upon the incidence of atherosclerosis. Generally such groups are economically underdeveloped, with a high infant and child mortality (which may remove susceptibles to atherosclerosis), a high level of energy expenditure, less sedentary habits, different work patterns, different goals and motivations, and not the same social stresses and tensions that characterize societies with a high consumption of animal fat.

Present Status. A major contribution of the nutritional hypothesis has been the removal of atherosclerosis from the stagnant pool of degenerative disease where the only pathogenic factor was aging. The concept most consonant with available facts is that atherosclerosis is a complex metabolic derangement, predisposed to by heredity and initiated and sustained by environmental factors. Its natural evolution is modified by a host of variables including diet, sex, age, hemodynamic factors, hemoglobin concentration, metabolic rate, level of activity, tobacco consumption, and psychobiologic stresses and strain.

Which is primary and which are ancillary elements in the constellation? Clinical as well as experimental observations suggest that there must be multiple causes. Two elements are now in the process of dissociation, the thrombotic and the atherogenic. Is the coronary artery occluded by a solitary thrombus with other vessels free of atherosclerosis, a facet of the same disease which manifests also diffuse and far-advanced atherosclerosis without thrombi? Attempts have been made to unify these two processes as an expression of the same lipid derangement. Yet, no well-established differences have been found to differentiate the clotting pattern of the coronary patients from that of the normal individual, even after fatty test meals. It may be that an appropriate test to show a difference has not been selected, or it may be that in vitro testing is not adequate to differentiate minor, yet critical, in vivo changes.

A problem that seriously complicates recognition of causal factors in human atherosclerosis, especially coronary artery disease, is that the disease is already far advanced when it surfaces to clinical view. Frequently it is in the end stages of its evolution. What is being studied clinically are the consequences of the pathologic process, not the process itself. What is operative at these stages of the disease may not necessarily be true at the onset. There is clinical evidence that with advanced coronary disease a high fat intake may be detrimental. Does this also hold at the inception of the disease? Until the coronary lesion is visualized during life and the environmental factors affecting its evolution are disentangled, a precise definition of its cause or causes may not be possible.

Therapeutic Implications. Whether or not a disease is fully comprehended, the physician must treat his patient. Therapy, if it is to be other than merely symptomatic, must avail itself of nutritional findings. With the prevalence of atherosclerosis, a proper question is, "Who should be treated?" As yet, however, there is no method for the clinical recognition of early coronary, cerebral, or renal atherosclerosis. Biochemical methods do not suffice to distinguish persons with occult disease. Furthermore, no conclusive evidence exists that dietary modifications, specifically alterations in the quality or quantity of lipid intake, affect the human atheromatous process. It follows that, for the present, there is no justification for a general modification of the American diet.

In the present state of our knowledge it is reasonable to limit nutritional therapy to certain patients already affected with the clinical sequelae of atherosclerosis or having a strong family history of cardiovascular disease. Obviously patients who exhibit a lipid abnormality in the absence of any recognizable atherosclerosis should be treated in view of the greater hazard of coronary heart disease than exists among patients without such abnormality.

If serum lipid concentrations are to be altered, it is important to know which fraction best characterizes the derangement of fat metabolism with the highest association with coronary artery disease. Differences of opinion exist on this point. The individual patient cannot be characterized as a potential victim of atherosclerosis solely by a determination of any of the serum lipids. Of the various tests employed, the serum cholesterol appears to be as good as any other test. It has the double advantage of relative simplicity and cheapness. The serum lipoproteins do not aid further in differentiating diseased from

healthy individuals. The widespread clinical determination of these fractions is, therefore, not justified.

What then constitutes a "normal" or "desirable" cholesterol level? This is not an easy point to establish. The concept of normality is usually derived from what is average or generally prevalent. But the average level is not necessarily a desirable level. In view of the fact that atherosclerosis is endemic in this country and, by implication, lipemia is widespread, deriving the normal cholesterol from averaging an American population may give rise to erroneously high results. If a figure is to be entertained, it can be argued with some merit that a normal serum cholesterol level for the adult should be in the neighborhood of 150 mg. per cent. This is of the order of magnitude noted in children, young women, primates, and in societies that have a paucity of coronary artery disease. A recent study showed that 83 per cent of 171 American men between the ages of 40 and 59 who developed myocardial infarctions had serum cholesterols of 212 mg. per cent or higher.[3] This latter figure may constitute a more practical clinical objective for Americans.

Even if a certain concentration of cholesterol constituted a well-defined therapeutic objective, the problem still exists as to the accuracy of the biochemical determination. Determinations of cholesterol do not always give closely reproducible results, even in duplicate determination. Patients with highest cholesterol levels have the greatest degree of variability. A single cholesterol determination is adequate to insure a value within 15 mg. per cent of the true mean value two thirds of the time. A sample size of 2 would insure a value within 10 mg. per cent of the true mean two thirds of the time.[4] It is important also to recognize that great variability exists between different laboratories. The physician must be acquainted with the performance and reproducibility in results of the laboratory he selects. It is best to have at least 2 control determinations on separate samples of serum before launching any therapeutic program to correct an elevated level of serum cholesterol. Reduction of the level should be regarded as certain only when the result is sustained and the reduction exceeds at least 50 mg. per cent.

How then is the cholesterol level to be lowered? It is to be stressed that loss of weight per se may achieve a reduction in cholesterol. In the patient with a cardiac problem, loss of weight may be beneficial, independent of the lipid change. Lowering the total fat intake is the most effective way of reducing calories and thus reducing weight. A number of ancillary methods for reducing cholesterol probably are ineffective if weight is simultaneously gained. An increasing number of measures is being made available to the physician in his combat with cholesterol. Nicotinic acid, the beta sitosterols, and polyunsaturated fatty acids are receiving extensive study. The most significant reduction of cholesterol concentration has been achieved in patients on rigid formula diets where fats high in polyunsaturated fatty acids such as corn or cottonseed oils were substituted for other fat components. When fats rich in polyunsaturated fatty acids are merely added to the diet, a weight gain may follow and the cholesterol, perhaps not lowered at all, may even be increased. Thus in treating the patient who has clinically manifest atherosclerosis and an elevated cholesterol value, the weight should be lowered by less total calories, less total fat. Such fat as is consumed should be rich in linoleic and arachidonic acids. When such a program is coupled with moderate exercise, a lowering of the serum cholesterol levels will generally follow. There is no assurance, however, that this will have any salutary effects on the far-advanced atherosclerotic process.

A Further Appraisal. The validity of a theory is determined by the economy of its suppositions, by its predictive power, and by its comprehension of available relevant facts. Based on these criteria, the nutritional hypothesis does not constitute the definitive theory of the pathogenesis of atherosclerosis. Any

sound theory will have to assimilate a number of biologic facts which have thus far not been adequately clarified.

While atherosclerosis has no doubt plagued man for millenia, its present widespread incidence may reflect profound changes in human life. As man's lifespan expanded, processes emerged that were not filtered through the fine sieve of organic evolution. This was necessarily so, for there exists no mechanism by which natural selection can operate beyond the phase of reproduction. In effect, nature is absolutely indifferent to individual survival once the reproductive phase is over. Two implications follow: first, that the biologic changes which predispose to such diseases as atherosclerosis have not been culled from the stream of inheritance by rigorous evolutionary process; second, that adaptive and compensatory reactions, which are stratgems of natural selection, have not developed. It is therefore to be expected that genetic factors are implicated in human atherosclerosis. Does this mean, then, that man's new-won freedom to an increased lifespan contains within it the inexorable forces that are ultimately destructive of life?

Hereditary factors are not authoritarian determinants of the developmental process. What emerges is conditioned ultimately by the external as well as the internal environment. It is clear that body and environment are in continuous determining relations. For the foreseeable future man will attempt to cope with deleterious genetic factors by modifying his environment.

Environment provides not only the food intake but also the data for sensory intake. This total perception, channeled through the central nervous system, continuously influences every bodily process. In man not only immediate sensation but also the reprojection of sensation within the interpretive areas of the brain, as modified by cultural patterns and social relations, becomes an objective condition affecting bodily function and even biologic integrity. The exploration of the impact of psychobiologic factors upon human biochemistry and physiology is in its earliest stages.

Of the many environmental factors that play a role in atherosclerosis, nutrition is undergoing extensive exploration. The diverse diets that now are found among different peoples reflect profound differences in ways of life. Thus, diet is not readily isolated from the matrix of man's total transaction with his environment. Progress in atherosclerosis may be most rewarding by approaches that combine both the tools of nutrition and psychobiology.

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Surgical Treatment of Atherosclerotic Occlusive Lesions in Patients with Cerebral Arterial Insufficiency

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Cerebral vascular disease, according to the results of arteriography, may be caused by extracranial arterial lesions in one third of the cases. Observations in 174 cases are described. The results of surgical treatment in 63 patients are presented and evaluated on the basis of restoration of circulation, clinical improvement, and survival. The implications regarding diagnosis and indications and contraindications for surgery are discussed.

IT IS now well established that cerebral arterial insufficiency may often be caused by atheromatous occlusive lesions located in the extracranial portions of the arteries supplying the brain.[1-13] Although its incidence has not been accurately determined, more extensive application of arteriography in the study of such patients suggests that this type of occlusion occurs in more than one third of the cases of cerebral arterial insufficiency. While the occlusive process may be variable in its pathologic features, it tends to assume certain characteristic patterns, particularly as to location, with the most frequent sites being at the origins of the internal carotid, innominate, left common carotid, and vertebral arteries. Multiple lesions are frequent, occurring in 40 per cent of the cases. The limitations of collateral circulation imposed by this frequency of multiple arterial involvement, the progressive nature of the occlusive process, and the dismal prognosis resulting from conservative therapy emphasize the desirability of a more direct attack designed to restore normal blood flow and preserve cerebral function.

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Fortunately, these lesions are well localized with the artery being relatively normal both proximal and distal to the occlusion, particularly in the early stages of the disease. These pathologic features of the lesion have led to the application of certain operative procedures that have proved effective in the treatment of similar lesions occurring elsewhere, namely, the aorta, and the iliac, femoral, and popliteal arteries.[3, 5-7, 11, 13, 14] The well-localized lesion may be removed by endarterectomy. In other instances when the lesion is more extensive, the occlusion may be bypassed with a graft. Following the successful application of this direct surgical approach in a patient with occlusion of the left carotid artery on August 7, 1953, we have employed this form of therapy in the treatment of 88 lesions occurring in patients with cerebral arterial insufficiency, and this report is concerned with an analysis of these cases.

Clinical Material

Arteriographic studies were performed in 174 consecutive patients with the clinical manifestations of ischemia of the brain or upper extremity. Extracranial arterial occlusion was demonstrated in 73 patients (42 per cent). Operation was employed in the treatment of 63 of these patients, and those cases form the basis of this study. The remaining 10 patients are excluded because they had complete occlusion of the internal carotid artery of long duration, which extended well into the intracranial portions of the artery. In the light of experience obtained early, these cases were considered inoperable on the basis of the arteriographic findings.

Pathology

A total of 115 extracranial arterial occlusive lesions occurred in the 63 patients submitted to operation. The limitations of collateral circulation in these cases were emphasized by the presence of multiple lesions in 32 patients (50 per cent). Of the 115 lesions, 78 were explored surgically (table 1). The remainder were considered to be inoperable either due to the extent of occlusion or are to be treated later. Circumstances favorable for restoration of circulation were found at exploration of 75 lesions. The unfavorable lesions were all completely obstructive and were located in the internal carotid arteries. The extent of the lesion in the latter cases was apparent in the arteriograms before operation and each was suspected to be inoperable on the basis of the duration of the disease. These cases were treated early in the series when the extent of operability was unknown. In the light of present knowledge, these cases would now be considered inoperable on the basis of the arteriograms and the clinical manifestations of the disease.

The obstruction was due to atherosclerosis in all cases and, when incomplete, was limited to a discrete atheroma near the origin of the involved vessel (fig. 1). Complete obstruction occurring in the more advanced cases was produced by superimposed thrombosis, and the lesions in these patients consisted of the atheroma and thrombus in various stages of organization (fig. 2). Incomplete occlusions were always well localized, with the artery being reasonably normal both proximal and distal to the lesion. Complete occlusions were usually more extensive, and when located in the internal carotid or vertebral arteries, extended well up into the intracranial portion of artery in 75 per cent of the cases. Complete occlusions of the great vessels arising on the aortic arch, although frequently extensive, never extended into the intracranial arterial segments and were always associated with reasonably normal patent vessels outside the skull, both proximal and distal to the obstruction. These pathologic features of the lesion permitted the application of direct operation in all cases of occlusion located in the great vessels arising on the aortic arch regardless of the nature and extent of the lesion. Incomplete occlusions of the internal carotid and vertebral arteries were similarly susceptible to operation. Complete occlusions at the latter levels, however, were rarely operable unless treated soon after occlusion became complete.

Table 1.—*Occlusive Disease of Innominate, Carotid, Subclavian and Vertebral Arteries*

Location of lesion	Complete			Incomplete		
	No. explored	No. with operable lesions	No. circulation restored	No. explored	No. with operable lesions	No. circulation restored
Internal carotid	17	5	5	33	33	32
Common carotid	6	6	6	3	3	3
Innominate	4	4	4	4	4	4
Subclavian	10	10	10	5	5	5
Vertebral	2	1	1	4	4	2
Total	39	26	26	49	49	46

Clinical Manifestations

The ages of these patients ranged from 24 to 71 years, with the highest incidence in the fifth, sixth, and seventh decades. There were 50 men and 13 women in this series of patients. There was no particular correlation between age and sex incidence and the location of the lesion, except that the younger patients had occlusions of the great vessels arising on the aortic arch, and 6 (49 per cent) of the 13 women in this series had lesions at this level. The relatively high incidence of hypertension and heart disease in this form of occlusive disease is similar to that recognized for occlusive disease of the lower extremities. Patients having blood pressures of 150/90 mm. Hg or greater were considered to be hypertensive. On this basis, 26 patients (40 per cent) were found to be hypertensive with little or no relationship in this regard to the location and extent of the lesion. Some form of heart disease, usually previous myocardial infarction,

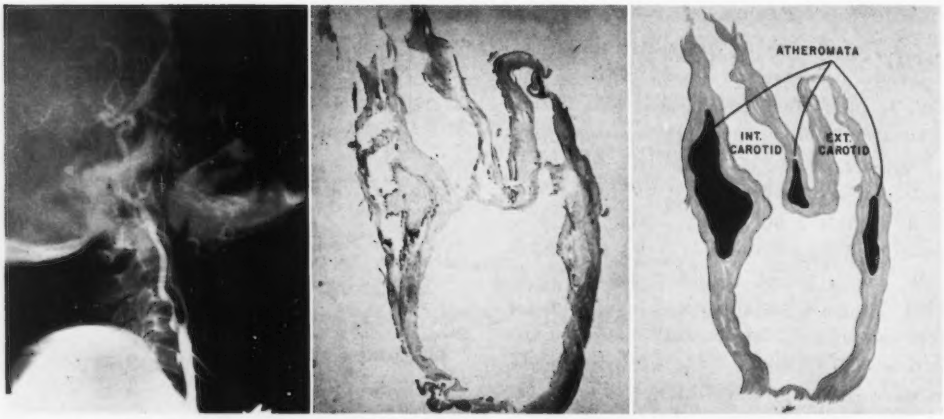

FIG. 1 *Left.* Carotid arteriogram performed before operation. *Middle.* Photomicrograph. *Right.* Diagram of specimen removed at operation showing incomplete occlusion of internal carotid artery by discrete atheromata located at origin of artery.

was found to be present in 19 patients (30 per cent). Associated atherosclerotic occlusions of the aorta and the iliac, femoral, and popliteal arteries were present in only 5 patients (7 per cent).

The clinical manifestations of arterial insufficiency in these patients varied with the location and extent of the occlusive process and for convenience are considered separately.

INTERNAL CAROTID ARTERY OCCLUSION (INCOMPLETE)

Patients with incomplete occlusions of the internal carotid arteries had had one or more attacks of cerebral arterial insufficiency ranging from a brief period of mild weakness or paresthesia to complete hemiplegia with total aphasia. Complete or near complete recovery had occurred in over half of the cases by the time of operation. In 4 patients who had not had previous attacks, persistent complete paralysis occurred, with aphasia in 3. Other neurologic deficits occurring in this group of patients were monocular visual defects, mental obtundity, and headache. Two patients complained of ear noises that occurred synchronously with the pulse.

The physical findings in these patients were limited to the neurologic defect, when present, and certain changes in the carotid arteries. A systolic murmur could be heard under the angle of the jaw in all patients with partial occlusions of the internal carotid arteries, and, as previously indicated, 2 patients heard these murmurs with each heart beat. Two patients with contralateral partial occlusions of the carotid artery developed transient loss of consciousness with carotid compression in the neck. The atheromatous lesion itself could be palpated as a firm mass in the region of origin of the internal carotid in several cases. In most instances, the region of the bifurcation was less flexible than in the normal patient. Pulsations in the neck, throat, and face were normal in patients with partial occlusions at this level, since the external carotid artery remained patent in all cases.

INTERNAL CAROTID ARTERY OCCLUSION (COMPLETE)

The history of illness in patients with complete occlusion of the internal carotid artery was in general considerably longer than in those with partial occlusions. Almost all patients in this series with persistent hemiplegia of long duration were in this group. Persistent neurologic deficits, usually in the form of paralysis, were present in all these cases. The final episode had been preceded by multiple transient attacks in 80 per cent of the cases,

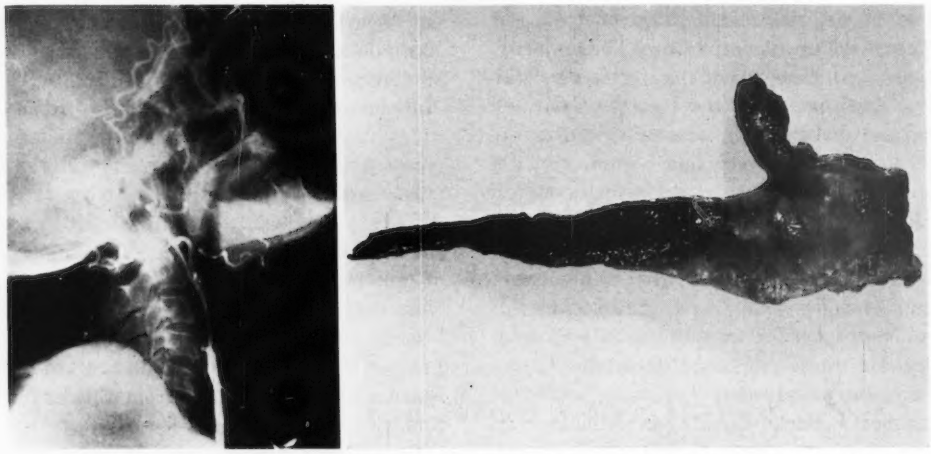

FIG. 2 *Left.* Preoperative carotid arteriogram. *Right.* Specimen removed at operation showing complete occlusion of internal carotid artery by thrombus superimposed on atheromatous lesion.

thus indicating the progressive nature of the disease. Peripheral neurologic deficits were demonstrated in all cases and ranged from mild speech or mental impairment to complete hemiplegia, aphasia, or coma. The degree of neurologic impairment was in many respects related both to the duration and extent of the disease. For example, the degree of paralysis was usually greater in patients who had not had previous attacks and in those with bilateral lesions. There were several exceptions, and the most impressive of these occurred in 2 patients who had bilateral complete occlusions of the internal carotid arteries. The neurologic deficits were mild in both of these cases and consisted of recurrent seizures, mental obtundity, minimal speech impairment, and weakness. Paralysis was more complete in the other patients with bilateral lesions, and the third patient in this series with bilateral complete occlusion had severe paralysis and was in coma.

Complete occlusion of the internal carotid artery in the neck was not evident in these patients on clinical grounds; however, it was suggested by the production of syncope by contralateral carotid compression. Carotid pulsations were always present in the neck, and although these were thought to have been diminished in some instances, there was no significant variation from the normal range of pulse volume. Arterial pulsations in the face, throat, and contralateral carotid artery were normal, and therre were no bruits unless there was partial occlusion of the ipsilateral external carotid artery.

Occlusion of Vertebral Arteries

Patients with vertebral artery occlusions presented the clinical picture previously described as basilar artery thrombosis, which consists of visual (cortical), cerebellar, cranial nerve, and peripheral motor and sensory disturbances. The symptoms were transient in some, but in other cases neurologic defects persisted. The patients who had recovered from their attacks showed no abnormal physical signs. Those with persistent defects showed disturbances in equilibrium, diplopia, bilateral blindness or hemianopsia, and bilateral sensory and motor impairment. The location of the lesion could not be determined in these cases by physical examination alone.

Occlusions of Great Vessels Arising on Aortic Arch

The clinical features of occlusive lesions in the great vessels arising on the aortic arch

consist of arterial insufficiency of both the brain and the upper extremities. The majority of patients with lesions of the common carotid arteries had had transient attacks of paralysis, visual disturbances, dizziness, and headache; however, recovery had occurred in all instances. Patients with occlusive lesions of the innominate and subclavian arteries had intermittent claudication of the upper extremities, and 3 of these patients had gangrenous changes of the fingers. Transient mild symptoms of basilar artery insufficiency had occurred in those patients with bilateral subclavian artery occlusion.

The most important finding in patients with lesions at this level was diminished or absent pulses in the neck and upper extremities. Loud systolic murmurs were present in the base of the neck and supraclavicular regions of patients with incomplete occlusions at this level. The combination of cerebral and upper extremity symptoms with pulse changes in the neck and pulse and blood pressure changes in the arms permitted reasonably accurate clinical localization of the lesion. The absence of pulsations indicated complete occlusion, while diminished pulsations or the presence of systolic murmurs in the base of the neck or supraclavicular region were associated with partial occlusion.

Diagnosis and Selection of Patients for Operation

A history of transient attacks, presence of systolic murmurs, syncope with unilateral carotid compression, and alterations in the carotid and subclavian pulses was highly suggestive of extracranial arterial occlusion; however, because of the inconsistency of these findings in patients with extracranial lesions, the precise location and extent of the occlusion were determined by special examination. Several types of examination have been employed for this purpose, namely, electroencephalography, ophthalmodynamometry, and arteriography. Abnormal electroencephalographic patterns were observed in patients with extracranial occlusions who had persistent neurologic deficits indicating residual brain damage. The findings in these cases were similar to those produced by intracranial occlusions and, consequently, were of little significance in the localization of the lesion. In many patients with extracranial arterial occlusions, abnormal electrical activity was produced by contralateral carotid artery compression or sudden elevation of the upper part of the body. Unfortunately, these changes were not produced in all patients with these lesions, and although highly significant when present, the precise location and extent of the lesion were not apparent from this examination.

Ophthalmodynamometry is an indirect method of measuring the retinal arterial blood pressure, which is dependent upon normal intra-ocular blood flow. Under normal circumstances, the major blood supply to the inside of the eye is derived from the ophthalmic artery, which is an intracranial branch of the internal carotid artery. A small part of the intra-ocular arterial blood flow under normal conditions is provided by the orbital branches of the internal maxillary artery, a major branch of the external carotid artery. The eye, therefore, has an extracranial and an intracranial source of arterial blood flow, both of which are amply connected by collateral channels. The external carotid artery is rarely involved by the occlusive process, and, in our experience, ocular arterial blood flow through these extracranial channels apparently increases as that in the intracranial segment decreases, not only providing normal ocular blood flow but significant collateral blood flow to the cerebrum through the ophthalmic artery. Consequent to the adequacy of this collateral blood flow to the eye, intraocular pressure is frequently normal in patients with extracranial arterial obstruction. For these reasons, this particular method of examination is not entirely reliable. Moreover, the precise location and extent of the lesion is never evident by this method alone.

Arteriography was the most important method of study in these cases. In fact, it

was impossible to determine precisely the location and the extent of the lesion when located in the internal carotid and vertebral arteries by any other method. Although occlusion of the great vessels on the aortic arch could be determined on clinical grounds in many instances, arteriography was essential in some for precise determination of the location and extent of the lesions. The technics of arteriography vary according to the particular artery involved, and these are discussed separately.

Angioaortography

The thoracic aorta and great vessels arising on the aortic arch were visualized, as described by Robb and Steinberg,[15] in patients with arterial insufficiency of the cerebrum and upper extremities, particularly in the presence of murmurs in the base of the neck or diminished pulses in the neck and upper extremities.[4] The procedure is performed under local anesthesia. A Robb-Steinberg cannula is inserted percutaneously into an antecubital vein, and the arm-to-tongue circulation time is determined by injecting 50 ml. of 0.8 per cent Decholin solution. A similar volume of 85 per cent sodium diatrizoate (Hypaque) solution is injected, and roentgenographic exposure is obtained of the chest and lower neck in the left anteroposterior oblique position after delaying an interval equal to the arm-to-tongue circulation time. Good visualization has been obtained by this method, and the occlusive lesions are seen in the great vessels originating near their origin from the aortic arch and extending distally for varying distances. This procedure has been performed in over 250 patients for various lesions (including aneurysms) at this level with no mortality or significant complications.

Carotid Arteriography

Bilateral percutaneous carotid arteriograms, as described by Egas Moniz,[16] are performed in all patients with cerebral arterial insufficiency in the regions of the anterior and middle cerebral arteries who do not have the clinical signs associated with lesions in the great vessels arising on the aortic arch.[4] This study is performed as soon as possible after an attack of cerebral arterial insufficiency, and, should neurologic deficits persist, it is undertaken as an emergency examination. The procedure is performed under local anesthesia. A Cournand needle is inserted into one common carotid artery low in the neck. A flexible tube is attached to the needle, and with a 30-ml. syringe, 8 ml. of 50 per cent Hypaque solution are injected. Roentgenographic exposure is obtained of the head and neck in the lateral position during the latter part of the injection. The procedure is then repeated on the opposite side, since bilateral lesions occur in 25 per cent of the cases. This study has been performed in 160 patients without mortality, significant discomfort, or complications. An important consideration in these cases is the fact that the disease process has not advanced as a result of the examination. Incomplete occlusions of the internal carotid artery appeared as defects in the outline of the internal carotid near its origin. When occlusion of the internal carotid artery was complete, the extracranial segment of this vessel did not appear in the roentgenogram. All patients with incomplete occlusions were considered candidates for operation. However, patients with complete occlusions at this level are now considered operable only when the symptoms suggest very recent complete occlusion.

Vertebral Arteriography

Bilateral vertebral arteriography is performed in all patients with the clinical manifestations of basilar artery insufficiency.[3, 4] Since the lesions occur in the vertebral arteries near their origin from the subclavian artery, it is necessary to visualize both the subclavian artery and the vertebral artery. The procedure is performed under local anesthesia by inserting a Cournand needle into the subclavian artery in the supraclavicular space. A flexible tube is attached and 20 ml. of 50 per cent Hypaque solution are injected. Roentgenographic exposure is made of the head, neck, and upper thorax, with visualization of the

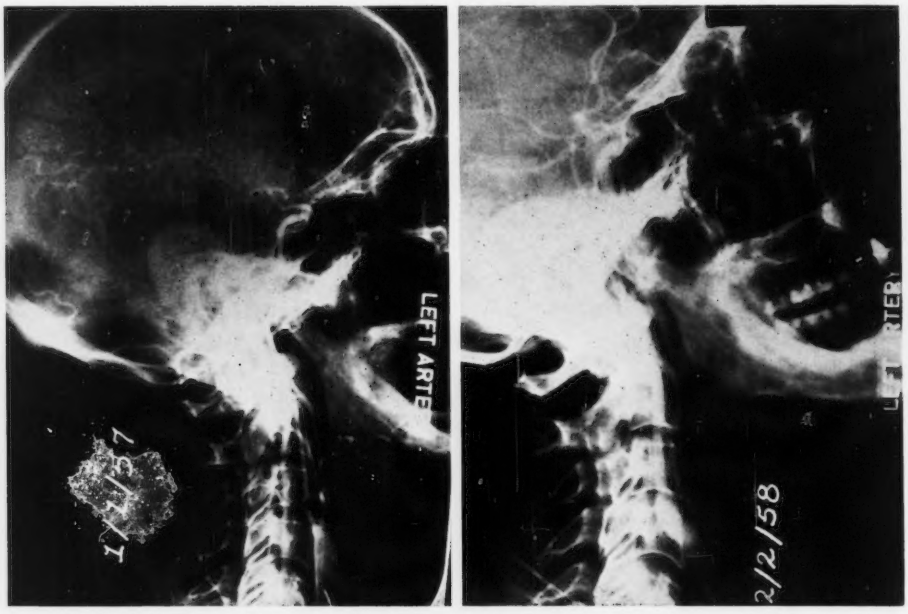

FIG. 3 *Left.* Preoperative carotid arteriogram showing partial occlusion of internal and external carotid arteries at their origin. *Right.* Carotid arteriogram made 13 months after operation showing restoration of normal blood flow.

subclavian, vertebral, and basilar arteries and their branches. This procedure is then repeated on the opposite side in view of the frequency of bilateral lesions. This procedure has now been performed in 30 patients without mortality; however, pneumothorax has occurred in 20 per cent of the patients. This complication has been satisfactorily relieved in all cases by simple aspirations of the chest. Patients with partial occlusions are considered ideal candidates for operation. Complete occlusions are considered inoperable unless a patent distal segment is present in the neck or the occlusion is of recent onset.

TREATMENT

Treatment in these patients was directed toward restoration of a normal pulsatile blood flow to the brain beyond the occlusion to relieve symptoms or prevent further difficulty. Two types of procedures were employed for this purpose, namely, endarterectomy and end-to-side bypass graft. Endarterectomy was employed in the treatment of lesions that were discrete and well localized to a short segment of artery 1 to 2 cm. in length (figs. 3 and 4). The technical application of this procedure varied with the artery involved. For example, internal carotid artery occlusions were removed either through a transverse incision made in the common carotid artery immediately proximal to the origin of the internal carotid or through a longitudinal incision made in the internal carotid artery in the region of the atheromatous obstruction. Because of the small size of the vertebral artery, endarterectomy of this vessel was performed through an incision made in the subclavian artery opposite the origin of the vertebral artery by developing a plane of dissection under the intima of the subclavian artery and extending this dissection into the vertebral artery beyond the occlusion.[17] Endarterectomy of the great vessels arising from the aortic arch was performed by longitudinal incision in the involved artery in the region of obstruction.

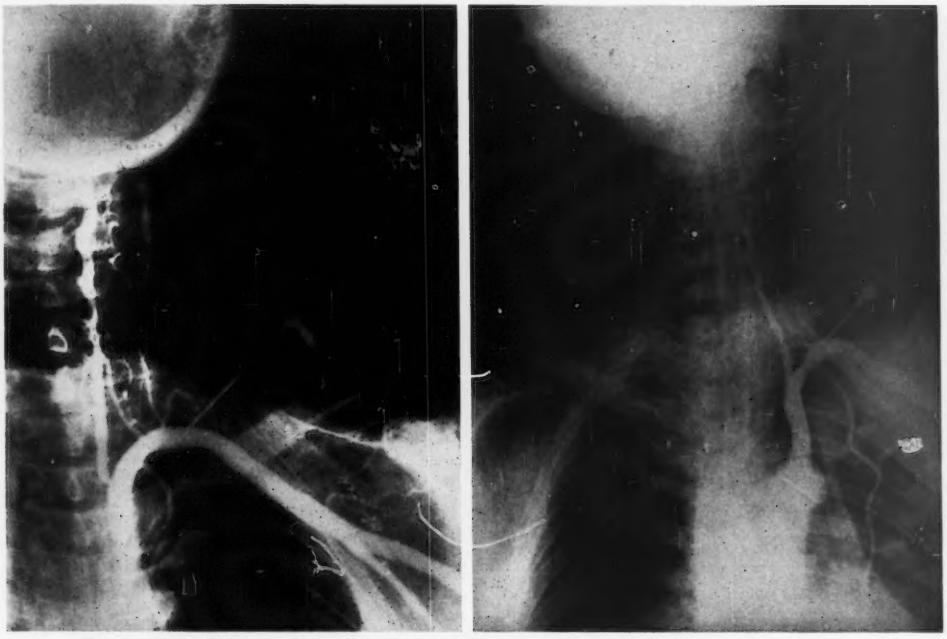

FIG. 4. *Left.* Preoperative subclavian vertebral arteriogram showing partial occlusion of vertebral artery at its origin from subclavian artery. *Right.* Postoperative arteriogram showing restoration of normal circulation.

The more extensive lesions were bypassed with use of a specially designed, flexible knitted Dacron tube.[17–19] In patients with internal carotid artery occlusions, one end of the tube was sutured to the uninvolved common carotid artery proximal to the lesion and the other end was sutured to the patent segment of internal carotid artery distal to the occlusion (fig. 5). The bypass graft in patients with vertebral artery occlusion extended proximally from the patent subclavian artery to the patent vertebral artery distal to the occlusion. In patients with occlusions of the great vessels arising from the aortic arch, the proximal end of the tube was sutured to the side of the ascending aorta and the other end was sutured to the carotid or subclavian artery distal to the obstruction (fig. 6). In the latter cases, either straight, bifurcated, or even trifurcated tubes were employed, depending upon the number of vessels involved.

In this series of 75 segmental lesions, the obstruction was well localized and endarterectomy was performed in 37. The remaining 38 lesions, being more extensive, were bypassed with a flexible, knitted Dacron tube. Cerebral protection was rarely required during operation. The period of complete arterial occlusion during the procedure ranged from 5 to 30 minutes in these cases. Collateral circulation was sufficient to maintain normal function during this period except in patients submitted to operation for partial occlusion of the internal carotid artery in the presence of complete occlusion on the other side. Patients with this combination of lesions required cerebral protection during operation, and temporary bypass shunts were successfully employed for this purpose. Reductions in blood flow were prevented by elevating the peripheral blood pressure to 200 mm. Hg, with use of a dilute solution of neosynephrine and with injection of the carotid sinus with procaine. Cerebral depression was prevented by the careful administration of such depressant drugs as opiates and barbiturates.

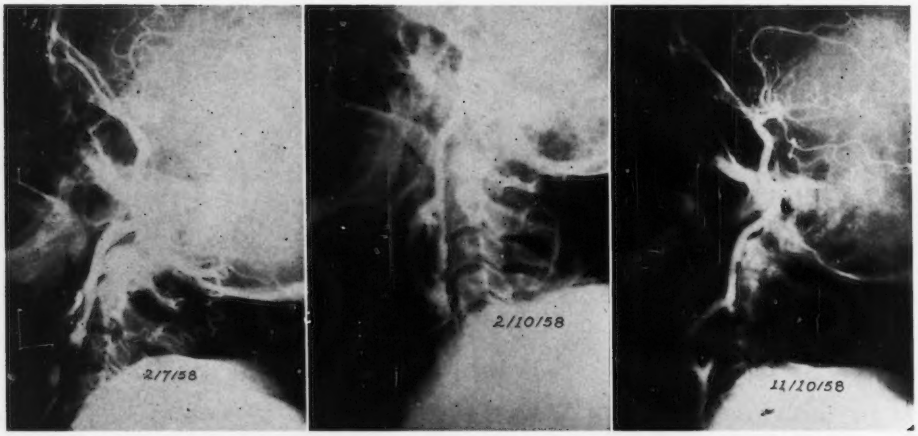

FIG. 5. *Left.* Preoperative carotid arteriogram showing partial occlusion of internal carotid artery near its origin. *Middle.* Arteriogram performed 3 days after operation showing functioning bypass graft. *Right.* Arteriogram performed 9 months after operation showing normal cerebral circulation through bypass graft and progression of bypassed lesion to complete occlusion.

RESULTS

Results of operation were evaluated on the basis of restoration of circulation, improvement or relief of symptoms, and survival. From an anatomic standpoint, proved by arteriography, circulation was restored in the treatment of all 75 segmental lesions except 3, 1 internal carotid artery and 2 vertebral artery occlusions (table 1). Circulation was restored in all cases with occlusion of the great vessels arising from the aortic arch regardless of the extent of the lesion and in all but 1 case with partial occlusion of the internal carotid artery. Circulation was also restored in all but 5 (25 per cent) of the patients selected for operation with complete occlusion of the internal carotid artery, and 3 patients (60 per cent) with occlusion of the vertebral artery. Circulation was not restored in any patient with complete occlusion of the internal carotid artery with persistent paralysis of more than 4 days' duration, unless operation was directed toward a contralateral partial occlusion. Cerebral circulation was made worse in only 1 case. This patient, treated early in the series, developed a right hemiplegia with aphasia 24 hours following endarterectomy performed by a technic no longer employed in these cases.

Severe cerebral arterial insufficiency manifested by coma and extensive paralysis was present before operation in 3 cases. These patients were submitted to emergency operation, and although circulation was restored in one or more of the occluded arteries, irreversible brain damage with extensive cerebral infarction had already occurred prior to operation and their fatal terminal course was not altered by operation. Death was due to myocardial infarction in 2 patients, 1 submitted to operation for gangrene of the fingers and the other for mental obtundity and recurrent convulsions. Death in the remaining case was due to hemorrhage resulting from infection and disruption of the suture line 10 days following operation.

The remaining 57 patients recovered from operation, and circulation was restored in one or more of the occluded vessels in 47 of the surviving patients. The functional response to treatment in these cases varied according to the location of the lesion and the condition of the patient before operation. Results were evaluated by clinical examination and listed

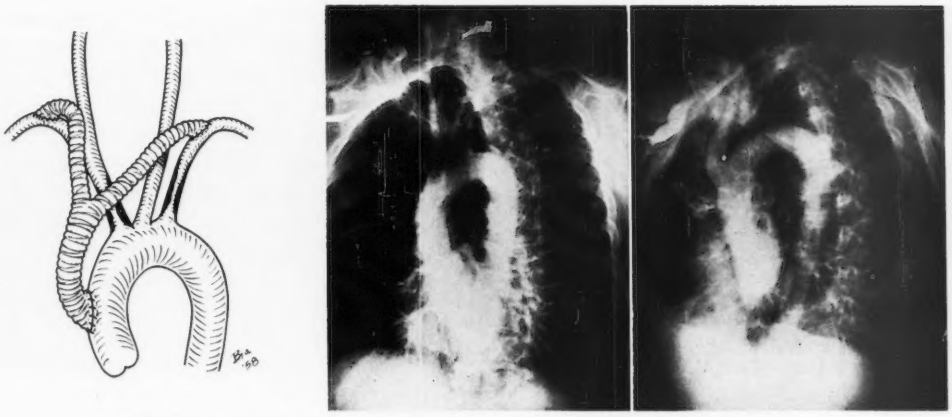

FIG. 6. Illustrations of case with occlusion of great vessels arising from aortic arch. *Left.* Diagrammatic drawing showing extent of occlusion (*black*) and bypass graft. *Middle.* Preoperative aortogram showing partial occlusion of innominate and left subclavian arteries. *Right.* Postoperative aortogram showing functioning bypass graft in place.

as worse, no change, significant improvement, or completely well. Persistent residual paralysis (hemiparesis or monoparesis) occurring before operation was improved in 5 cases and completely relieved in 8 patients. Progressive hemiplegia with aphasia of 18 hours' duration was completely relieved in 1 patient. Residual monocular visual defects (scotoma) were improved in 1 case and completely relieved in 4 patients. Homonymous hemianopsia was improved in 1 patient. Complete relief occurred from other symptoms: aphasia in 5, vertigo in 4, headache in 3, ear noise in 2, syncope in 1, and claudication of the arm in 17 patients. Transient attacks of paralysis (monoplegia or hemiplegia) have not recurred since operation in 13 patients who had completely recovered from such attacks before operation. All patients with lesions of the great vessels arising from the aortic arch were completely relieved and the majority of patients with lesions of the internal carotid or vertebral arteries were either relieved or significantly improved. In those patients in whom functional improvement did not occur, restoration of a pulsatile cerebral blood flow is considered likely to prevent progression of the disease. For example, bilateral internal carotid obstructions, incomplete on one side and complete on the other, were present in 4 of the patients in whom neurologic improvement did not occur following therapy. The neurologic deficit in these cases was of long duration and was due to the lesion producing complete obstruction. Cerebral function in these cases was dependent upon blood flow through the incompletely obstructed artery, since compression of the carotid on this side produced unconsciousness. In view of the progressive nature of the disease, eventual complete obstruction was anticipated; consequently, operation was directed toward the contralateral incomplete occlusion for prophylactic reasons.

The first patient in this series was operated upon a little over 5 years ago, and all cases have been carefully followed since discharge from the hospital with follow-up arteriograms being performed in most patients. The success achieved by operation has been well maintained in all but 4 patients. Death has occurred in 2 patients, one from myocardial infarction and the other from cerebral arterial insufficiency due to acute occlusion of the contralateral internal carotid artery; the one submitted to operation was still patent at autopsy. Recurrent occlusion has occurred in 2 patients with lesions of the internal carotid

artery in one and the left common carotid in the other patient. Endarterectomy had been employed in one and an end-to-side bypass graft had been inserted in the other. Both these cases were treated early in the series with technics no longer considered suitable in these cases.

Discussion

These observations in patients with cerebral arterial insufficiency indicating extracranial arterial occlusion in 42 per cent of them and the practical application of operative technics designed to restore normal circulation represent a departure from the usual concepts of the disease and its management. Although these lesions were described during the past century and arteriographic technics have been available for 25 years, cerebral arterial insufficiency resulting from extracranial arterial occlusion was considered rare. The importance and possible frequency of extracranial lesions was again emphasized in 1951 by Fisher.[8] The report by Eastcott and associates[6] in 1954 of relieving a patient with persistent cerebral arterial insufficiency by endarterectomy stimulated a lively interest in the subject, since this case suggested that direct operative therapy could be as effective in this disease as had been demonstrated in arterial insufficiency of the lower extremities. This interest, maintained by continued successful application of operative therapy, led to a more aggressive approach to the problem and a clearer understanding of the nature and incidence of the disease.

The atherosclerotic lesion is a progressive process that eventually consumes the arterial lumen and produces arterial insufficiency. Therapy not directed toward the lesion itself has become questionable. For example, 20 per cent of the patients in this series of cases were referred for operative treatment because satisfactory anticoagulant therapy had either not improved or not prevented progression of the disease. Moreover, 5 patients developed cerebral arterial insufficiency while their prothrombin times were being maintained at levels less than 10 per cent of normal by Dicumarol administration because of previous myocardial infarction. The successful results obtained by arterial reconstructive operations in the relief of persistent neurologic defects and the prevention of recurrent attacks, particularly in patients in whom anticoagulant therapy had failed, offer considerable hope in the future management of this problem with an otherwise dismal outlook.

The full potential offered by these new concepts may be realized by an aggressive approach. The limitations of diagnosis by clinical means must be taken into consideration and extracranial involvement should be suspected in all patients. Arteriography is essential for accurate diagnosis and should be routinely performed in all patients with cerebral arterial insufficiency. Every effort should be made to diagnose and treat the patient early in the course of the disease to prevent both the development of permanent brain damage and the progression of the disease. Operation for practical purposes may be considered invariably successful in patients with partial occlusions regardless of the extracranial location. The more advanced complete occlusions of the internal carotid and vertebral arteries, on the other hand, are considerably less susceptible to direct therapy unless submitted to operation soon after onset of complete occlusion. Immediate arteriography and operation are therefore necessary, particularly when neurologic signs persist, if the maximum number of these patients is to benefit from the reconstructive technics.

Summary

Arteriographic studies have been performed in 174 patients with clinical manifestations of cerebral arterial insufficiency. Extracranial arterial occlusion was demonstrated in 73 patients (42 per cent). Operation has been employed in the treatment of 63 of these patients who were found to have 115 occlusive lesions.

Occlusion of the great vessels arising on the aortic arch was manifested clinically by symptoms of arterial insufficiency of both the cerebrum and upper extremities and diminu-

tion or absence of pulses in the neck or arms. The precise location and extent of occlusion in patients with internal carotid and vertebral artery occlusion was evident only by arteriography.

At operation 75 lesions were found to be segmental in nature with a normal extracranial segment, both proximal and distal to the obstruction. Employing endarterectomy in 37 well-localized lesions and graft bypass in 38 more extensive occlusions, circulation was restored in 72 arteries. From an anatomic standpoint circulation was restored in all cases with lesions in the great vessels arising from the aortic arch, 97 per cent of those with operable lesions of the internal carotid artery, and 60 per cent of those with occlusions of the vertebral artery.

Severe cerebral arterial insufficiency manifested by coma and extensive paralysis was present before operation in 3 of these cases. Although circulation was restored in one or more of the occluded arteries, brain damage was persistent and the patients' fatal terminal courses were unaltered. Death in the remaining cases was due to myocardial infarction in 2 and hemorrhage in 1 case.

The remaining 57 patients recovered and circulation was restored in one or all of the occluded vessels in 47 patients. All patients with lesions of the great vessels arising from the aortic arch were completely relieved and the majority of patients with lesions of the internal carotid and vertebral arteries were either relieved or significantly improved. These patients have been followed up to periods of over 5 years, and the success achieved by operation has been well maintained.

Addendum

Since this article was submitted, operation has been employed in the treatment of an additional 61 lesions, making a total of 149. Of this number the internal carotid artery was involved in 93, the common carotid artery in 12, the innominate artery in 14, the subclavian artery in 21, and the vertebral artery in 9. All occlusive lesions involving the common carotid, innominate, and subclavian arteries were segmental in nature, and circulation was restored in all of them. The occlusive lesion was segmental in 83 of the 93 cases involving the internal carotid artery, and circulation was restored in 80. Of the 9 cases with vertebral artery occlusion, operation was successful in 6.

Summario in Interlingua

Studios arteriographic esseva effectuate in 174 patientes con manifestationes clinic de insufficientia cerebro-arterial. Extracranial occlusion arterial esseva demonstrate in 73 patientes (42 pro cento). Intervention chirurgic esseva usate in le tractamento de 63 de iste patientes in qui un total de 115 lesiones occlusive esseva constatate.

Occlusion del grande vasos a origine in le arco aortic se manifestava clinicamente in symptomas de insufficientia arterial tanto in le cerebro como etiam in le extremitates superior e in le diminution o le absentia complete de pulsos in collo e bracios. Le precise location e le extension del occlusion in patientes con occlusiones arterial interne carotidic e vertebral esseva evidentiate solmente per arteriographia.

Esseva constatate al operation que 75 lesiones esseva de natura segmental, con normal segmento extracranial tanto proximal como etiam distal con respecto al sito del obstruction. Endarterectomia esseva usate in le casos de 37 lesiones ben localisate, shunting per graffos in le casos de 38 occlusiones plus extense. Assi le circulation esseva restaurate in 72 arterias. In terminos anatomic: Le circulation esseva restaurate in omne le casos de lesiones del grande vasos a origine in le arco aortic, in 97 pro cento del casos de lesiones operabile del interne arteria carotidic, e in 60 pro cento del casos de occlusiones del arteria vertebral.

Sever grados de insufficientia cerebro-arterial, manifeste in coma e extense formas de paralyse, esseva presente ante le operation in 3 de iste casos. Ben que le circulation esseva restaurate in un o plures del occludite arterias, le injurias cerebral persisteva, e le mortal curso terminal del patientes remaneva sin alteration. Inter le altere casos, morte esseva causate per infarciemento myocardial in 2 e per hemorrhagia in 1.

Le remanente 57 patientes se restabliva. Le circulation esseva restaurate in un o omne vasos occludite in 47 de illes. Omne le patientes con lesiones del grande vasos a origine in le arco aortic experientiava un alleviamento complete. Le majoritate del patientes con lesiones del interne arteria carotidic e del arteria vertebral experientiava alleviamento o al minus grados significative de melioration. Le patientes remaneva sub observation postchirurgic durante periodos de usque a 5 annos, e le successo effectuate per le operation es ben mantenite.

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Functional Aortic Stenosis

A Malformation Characterized by Resistance to Left Ventricular Outflow without Anatomic Obstruction

By ANDREW G. MORROW, M.D., AND EUGENE BRAUNWALD, M.D.

When the clinical findings of aortic stenosis are present and a pressure gradient is demonstrated between the left ventricle and aorta, a discrete site of obstruction, generally amenable to surgical correction, has been assumed. The fallacy of this widely held concept is emphasized by the operative and hemodynamic findings in 3 patients described.

IT HAS generally been assumed that the demonstration of a systolic pressure gradient between the left ventricle and the aorta always results from stenosis of the aortic valve, the presence of a localized ring of fibrous tissue immediately beneath the aortic annulus (congenital subaortic stenosis) or, rarely, from a constriction of the aorta itself a short distance above the valve.[1, 2] These lesions are, in general, amenable to surgical correction and patients have been selected for operation on the basis of the magnitude of the pressure gradient across the stenotic orifice.[3] We have recently studied 2 patients in whom significant pressure gradients were demonstrated preoperatively but in whom no anatomic site of outflow obstruction could be detected at the time of open-heart operation. A third patient is described in whom functional obstruction to left ventricular outflow was demonstrated and found to regress gradually after the complete division of a discrete subvalvular stenosis. The clinical and hemodynamic findings in these patients are summarized in the present report.

CLINICAL SUMMARIES

Case 1. E. Z., a 27-year-old white man was asymptomatic until the age of 16 when he began to have precordial pain with severe exertion. At the age of 20 a precordial murmur was noted in the course of a routine physical examination. At age 25 exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea first appeared, peristed, and progressed in severity. Angina pectoris became more prominent and eventually disabling. In June 1957 he was studied by Drs. E. M. Nanson, L. Horlick, and J. E. Merriman at the University Hospital Saskatoon, Saskatchewan, where the clinical diagnosis of congenital aortic stenosis was made. Combined right and transbronchial left heart catheterizations demonstrated a normal cardiac index and a pulmonary artery pressure of 51/32 mm. Hg. In the course of left heart catheterization the catheter was passed into the aorta and upon being withdrawn traversed 2 zones of ventricular pressure. In the distal zone the pressure was essentially equal to the radial artery pressure but in the proximal one it exceeded the radial artery pressure by a mean systolic gradient of 95 mm. Hg. The left atrial and ventricular end-diastolic pressures were elevated to 20 mm. Hg. These findings were interpreted as indicative of the presence of subaortic stenosis.

In the ensuing year, the patient's symptoms progressed to some extent. He was admitted to the National Heart Institute in June 1958. There was no evidence of heart failure. The blood pressure was 120/70. The heart was enlarged and a prominent left ventricular lift was noted outside the midclavicular line. A faint, short systolic thrill at the apex was noted by only one of several examiners. No thrill was palpable at the base of the heart or in the carotid vessels. The rhythm was regular. The second heart sound was normally split with respiration. A grade IV holosystolic murmur was heard at the apex and along the left sternal border. A fainter, shorter ejection-type systolic murmur was heard at the base and radiated into the neck. A diastolic gallop and a short middiastolic murmur were present at the apex. The phonocardiogram is shown in figure 1. The electrocardiogram (fig. 2 *Top*) revealed left atrial and left ventricular hypertrophy. Fluoroscopic and radiographic examinations of the heart demonstrated slight generalized cardiac enlargement with prominence of the left ventricle (fig. 3). The

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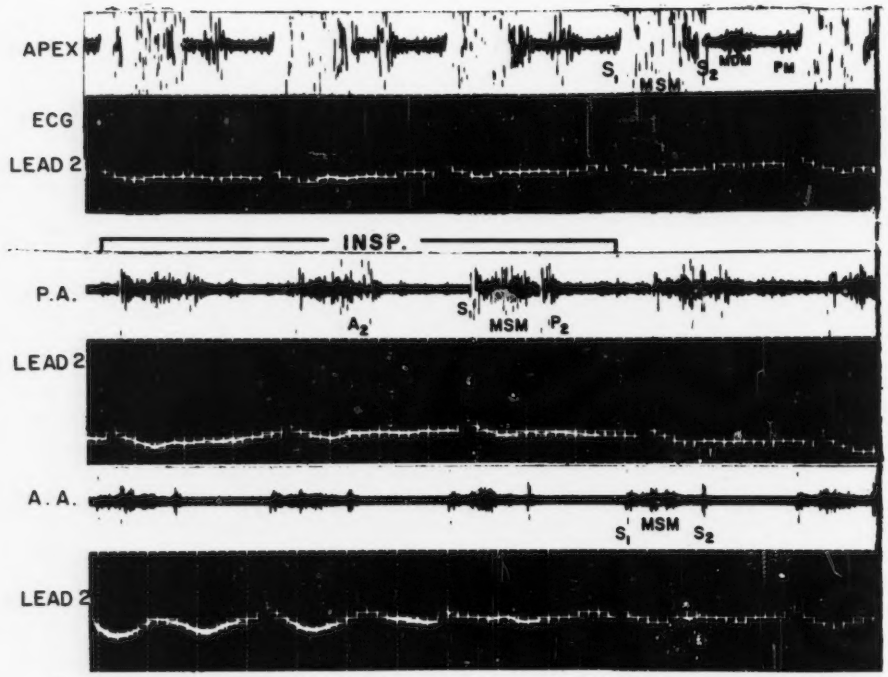

FIG. 1. Phonocardiogram of patient E.Z. S_1 and S_2, first and second heart sounds; *MSM* and *MDM*, midsystolic and mid-diastolic murmurs; *PM*, presystolic murmur; *A.A.* and *P.S.*, aortic and pulmonary areas respectively; A_2 and P_2, second aortic and pulmonary sounds.

ascending aorta did not appear to be dilated and no intracardiac calcification was noted.

The results of right heart catheterization are summarized in table 1. There was moderate elevation of the pulmonary artery pressure at rest and with exercise both the pulmonary arterial and pulmonary capillary pressures rose significantly. The cardiac output, normal at rest, did not rise normally with exercise. Left heart catheterization was carried out by the transbronchial route. The left atrial mean pressure was 16 mm. Hg and its contour was normal and did not suggest mitral valve disease. The catheter was manipulated into the aorta (pressure 118/71 mm. Hg) and upon withdrawal again traversed 2 zones of pressure with ventricular contour; in the distal one the systolic pressure was equal to that in the aorta. Proximally the ventricular pressure was 192/37 mm. Hg, resulting in a peak systolic gradient of 74 mm. Hg. The cardiac index at this time (indicator-dilution method) was 2.96 L./min./M.^{2} The calculated stenotic orifice area was 0.30 cm.^{2}/M.^{2} B.S.A.

A selective angiocardiogram with pulmonary artery injection revealed normal pulmonary vasculature and a normal-sized left atrium. The left ventricular cavity was small. No site of outflow

TABLE 1.—*Right Heart Catheterization*

Position		Pressure, mm. Hg, systolic/diastolic, mean	
		Patient E. Z.	Patient C. G.
PC*	Rest†	17/9, 12	14/11, 12
	Exercise	40/12, 26	
PA	Rest	45/10, 18	20/12, 15
	Exercise	60/22, 40	
RV		45/4	20/4 and 36/4
RA		5/1, 2	8/0, 4
PA N_2O test		1%	9%
Ventilation	Rest	4.05	3.70
L./min./M.^{2}	Exercise	9.90	——
QO_2 ml./min./M.^{2}	Rest	144	147
	Exercise	403	——
R. Q.	Rest	0.75	0.75
	Exercise	0.85	——
Cardiac index	Rest	3.11	3.00
L./min./M.^{2}	Exercise	4.29	——
Arterial O_2 saturation		95.8%	92.4%

*PC, PA, RV, and RA refer to pulmonary artery wedge position, pulmonary artery, right ventricle, and right atrium.

†Measurements in the resting state are the average of 2 determinations in every instance.

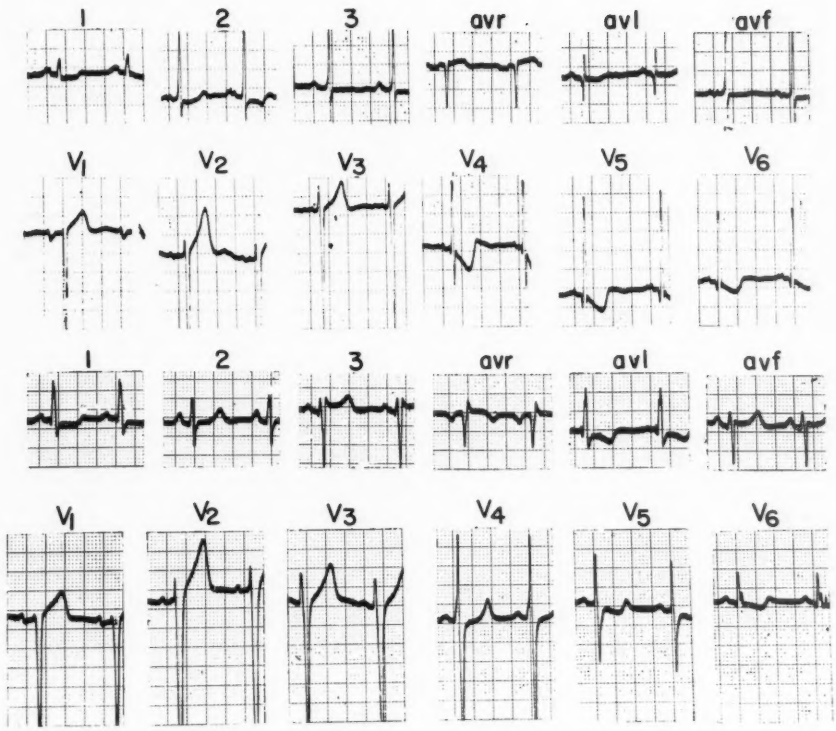

FIG. 2. Electrocardiograms of patient E.Z. (*Top*) and C.G. (*Bottom*).

obstruction could be visualized. The aorta was normal in size and contour.

On the basis of the studies outlined, the diagnosis of congenital subaortic stenosis seemed substantiated and operation for its relief was recommended and carried out on June 19, 1958. The aorta was of normal size and a systolic thrill of moderate intensity was felt within it. The left atrium was enlarged and tense and upon digital exploration of the mitral valve, moderate mitral regurgitation was palpable. The mitral leaflets were not thickened and palpation within the left ventricular inflow tract did not reveal a site of obstruction. With cardiopulmonary bypass and elective cardiac arrest induced with potassium citrate, the ascending aorta was widely opened. The aortic valve was normal and the leaflets were thin and mobile. No subvalvular stenosis was seen and a finger could be passed to the apex of the left ventricle with ease. The left atrium was then reentered and a bimanual examination of the entire ventricle carried out. Its wall was considerably thickened but no obstruction could be found and palpating fingers from the aorta and atrium met in the ventricular cavity. The left ventricular endocardium did not appear or feel abnormal. Postoperatively the patient's course was uncomplicated.

Case 2. C. G., a 20-year-old man, was first admitted to the National Heart Institute in July 1957 with the symptom of progressive exertional dyspnea. He was apparently normal at birth and in the course of many examinations by the family physician before the age of 12, the family was never told of the presence of a murmur. At this time, during a routine school examination, a murmur was detected and he was seen by a cardiologist who made the clinical diagnosis of ventricular septal defect. He had always complained of mild exertional dyspnea and this became gradually more severe after age 15. At about 14 he began to experience squeezing chest pain on exertion and he found it necessary to limit physical activity. He had had several attacks of vertigo but no true syncope.

Physical examination was normal except for the heart. The blood pressure was 110/70. The heart was enlarged with the apical impulse in the fifth intercostal space just within the anterior axillary line. There was a prominent left ventricular lift as well as a systolic thrill along the left sternal

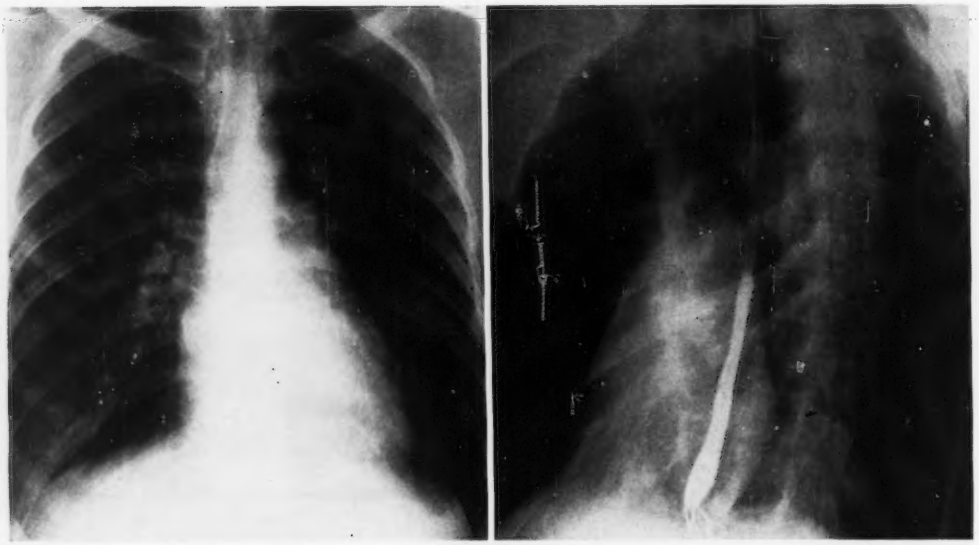

FIG. 3. Posteroanterior (*left*) and left anterior oblique (*right*) roentgenograms of patient E.Z.

border. No thrill was palpable to the right of the sternum or in the carotid vessels. The rhythm was regular and the second heart sound was louder in the aortic than in the pulmonic area. A harsh grade IV systolic ejection-type murmur (fig. 4) was best heard along the left sternal border and at the apex. It was less prominent over the aortic area and was only faintly heard over the neck vessels. A prominent protodiastolic gallop was heard at the apex. The electrocardiogram (fig. 2, *Bottom*) revealed left axis deviation and left ventricular hypertrophy. Fluoroscopic and radiographic examinations revealed moderate cardiac enlargement with fullness of the left ventricular and left atrial contours (fig. 5). There was no evidence of poststenotic dilatation of the aorta.

The results of right heart catheterization are summarized in table 1. The pulmonary artery pressure was normal and as the catheter was withdrawn across the outflow tract, the pressure contour indicated mild subvalvular pulmonary obstruction (fig. 6). Percutaneous puncture of the left ventricle was performed[4] and 2 distinct left ventricular systolic pressures were recorded, one equal to systemic pressure and one exceeding it by 75 mm. Hg. Following this procedure the patient developed cardiac tamponade which was relieved by the aspiration of 250 ml. of blood from the pericardial space. Subsequent left heart catheterization by the transbronchial route revealed a left atrial pressure of 14 mm. Hg (mean) and a normal pulse contour. The catheter was passed into the aorta where a pressure of 111/71 mm. Hg was recorded. Upon withdrawal, 2 distinct ventricular systolic pressures were encountered; distally the pressure was 113/20 and more proximally it was 185/20 (fig. 7). The cardiac index at this time was 3.63 L./min./M.^{2} and the calculated orifice area was 0.36 cm.^{2}/M.^{2} B.S.A. The preoperative diagnosis of congenital subaortic stenosis again seemed substantiated and operation was recommended but deferred for 1 year at the patient's request. In the year between study and operation the patient's symptoms and findings had remained unchanged.

Operation was carried out on August 15, 1958. Only a mild systolic thrill was palpable in the aorta which was of normal size and did not show poststenotic dilatation. No thrill was felt over the left atrium, which was somewhat enlarged. The mean left atrial pressure during operation was 20 mm. Hg. By direct needle puncture, a gradient of 50 mm. Hg between the inflow portion of the left ventricle and the radial artery was recorded. With the aid of total cardiopulmonary bypass and elective cardiac arrest the aorta was widely opened. The valve leaflets were entirely normal and palpation through the annulus did not reveal any subvalvular stenosis; a finger and a large Brock dilator could be passed with ease to the apex of the heart. The left ventricular wall was considerably thickened and there were prominent muscular trabeculations. The ventricular endocardium was not thickened. Following restoration of the circulation digital examination of the left atrium and mitral

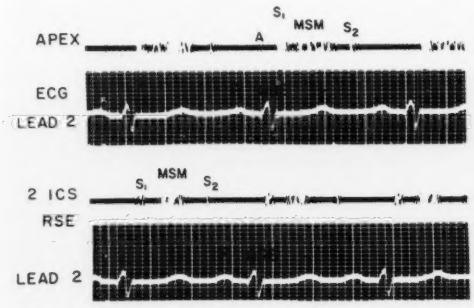

FIG. 4. Phonocardiogram of patient C.G. *2 ICS RSE*, placement of the microphone in the second intercostal space at the right sternal edge.

valve revealed normal leaflets and inflow portion of the ventricle. A mild jet of mitral regurgitation was noted. Postoperatively the patient's course was uneventful.

Three months after operation the patient returned for postoperative study. He felt well and his activity had been virtually unlimited. A selective angiocardiogram with left ventricular injection was carried out by the percutaneous method.[5] These films revealed an enlarged left ventricle and demonstrated incompetence of the mitral valve. The outflow portion of the ventricle appeared to become markedly narrowed in systole (fig. 8, *Top left*) but to open to some extent during diastole (fig. 8, *Top right*). The left ventricular cavity appeared in both projections to be encroached upon and almost divided by an intrinsic mass, presumably hypertrophied cardiac muscle (fig. 8, *Bottom*).

Case 3. J. R., a 16-year-old boy, was admitted to the National Heart Institute in August 1956. A heart murmur had been first noted at the age of 9 at which time he had first noted anginal pain. This had persisted, become incapacitating and had recently been accompanied by severe attacks of headache and vertigo. He presented the classic physical findings of aortic stenosis and in addition had a blowing decrescendo diastolic murmur along the left sternal border. The electrocardiogram revealed left ventricular hypertrophy and strain and x-rays showed left ventricular enlargement. There was poststenotic dilatation of the aorta. The results of right heart catheterization were normal. At transbronchial left heart catheterization the catheter was passed into the aorta where the pressure was 122/75 mm. Hg. Upon withdrawal it first traversed an area of left ventricle with a pressure of 122/15 and then entered the main ventricular cavity where a pressure of 244/15 mm. Hg was recorded. The peak systolic gradient was

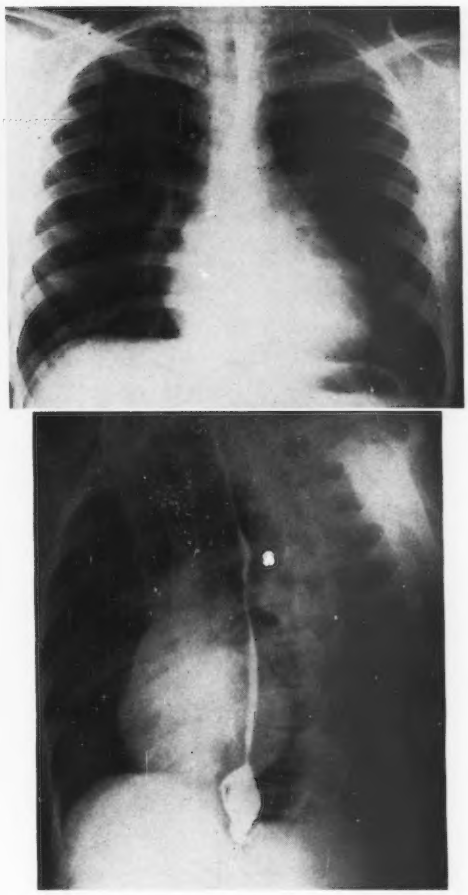

FIG. 5. Posteroanterior *(top)* and left anterior oblique (*bottom*) roentgenograms of patient C.G.

122 mm. Hg. An open-heart operation under general hypothermia was carried out on September 6, 1956. The aortic valve leaflets were not stenotic and a thin subvalvular fibrous ring just beneath the aortic annulus was divided and dilated, apparently completely. Three weeks after operation another left heart catheterization revealed the left ventricular pressure to be 193/8 mm. Hg and a gradient of 70 mm. Hg was still present. The patient's symptoms improved during a follow-up period of 18 months. At this time a third left heart catheterization demonstrated that the left ventricular pressure had fallen to a normal level, 115/7 mm. Hg, and that no gradient between the left ventricle and aorta existed. Representative pressure tracings obtained at the 3 left heart catheterizations are shown in figure 9.

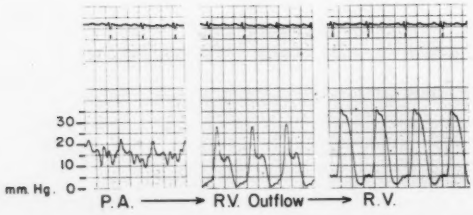

FIG. 6. Pressure tracings obtained in the pulmonary artery (*P.A.*), right ventricular (*R.V.*) outflow tract and main right ventricular cavity in patient C.G.

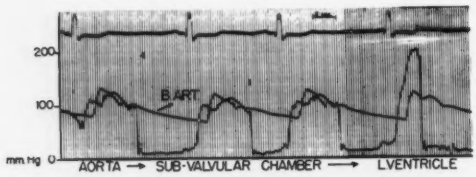

FIG. 7. Pressures recorded sequentially from the aorta, left ventricular outflow tract (subvalvular chamber), and main left ventricle in patient C.G. (*Reproduced by permission from Morrow, A. G., Braunwald, E., and Sharp, E. H.: Clinical features and surgical treatment of congenital aortic stenosis. Progress in Cardiovascular Disease* **1**: *80, 1958.*)

DISCUSSION

In the patients described, the hemodynamic evidence of obstruction to left ventricular outflow is unequivocal; in the first 2 patients a systolic pressure difference between the left ventricle and aorta was demonstrated on 2 separate occasions and was definitely localized to an area within the ventricle. On the other hand, it is equally evident that none of the usual forms of aortic stenosis is present since the absence of discrete supravalvular, valvular, or subvalvular obstruction was clearly proved at open-heart operation. In these 2 patients it must, therefore, be concluded that the obstruction to ventricular outflow is of such a nature that it is only operative in the contracting heart and was not apparent during the diastolic paralysis induced by potassium citrate. These features can only be explained by muscular hypertrophy of the left outflow tract of sufficient severity that flow is actually impeded during contraction.

Functional obstruction to ventricular ejection is not a new concept. A systolic pressure gradient across the outflow tract of the right ventricle may develop as a result of severe right ventricular hypertrophy associated with such lesions as stenosis of the pulmonary valve or ventricular septal defect.[6–11] Proof that this form of obstruction is secondary in nature is provided by the observations of Gasul et al.,[11] who noted its development in patients with ventricular septal defect and by the increasing number of reports of the regression of the subvalvular gradient when the primary stimulus to ventricular hypertrophy is removed by pulmonary valvulotomy.[6–10]

The development of similar secondary obstruction to left ventricular outflow was described by Brock.[12] He noted in certain patients with valvular aortic stenosis that even though a satisfactory valvular opening was apparently accomplished, a pressure gradient persisted after operation. This phenomenon was attributed by him to the occurrence of a muscular subvalvular stenosis in the grossly hypertrophied left ventricular outflow tract. Proof of the validity of this hypothesis is afforded by the catheterization data obtained in the third patient described in the present report. A substantial gradient was proved to persist after the anatomic obstruction had been abolished. It seems clear that this gradient was due to functional aortic stenosis since, with the gradual regression of the hypertrophy of the ventricle and without further mechanical intervention, it disappeared completely (fig. 9).

Another etiology of left ventricular hypertrophy resulting in functional aortic stenosis is systemic arterial hypertension. In 1 patient described by Brock[12] this seems clearly to be the case since severe systemic hypertension had been well documented in the patient's immediate history. He also postulated this mechanism in the other patient described in his report although an elevated arterial pressure had never been recorded. Hypertension can certainly not be invoked as the causative factor for the left ventricular hypertrophy

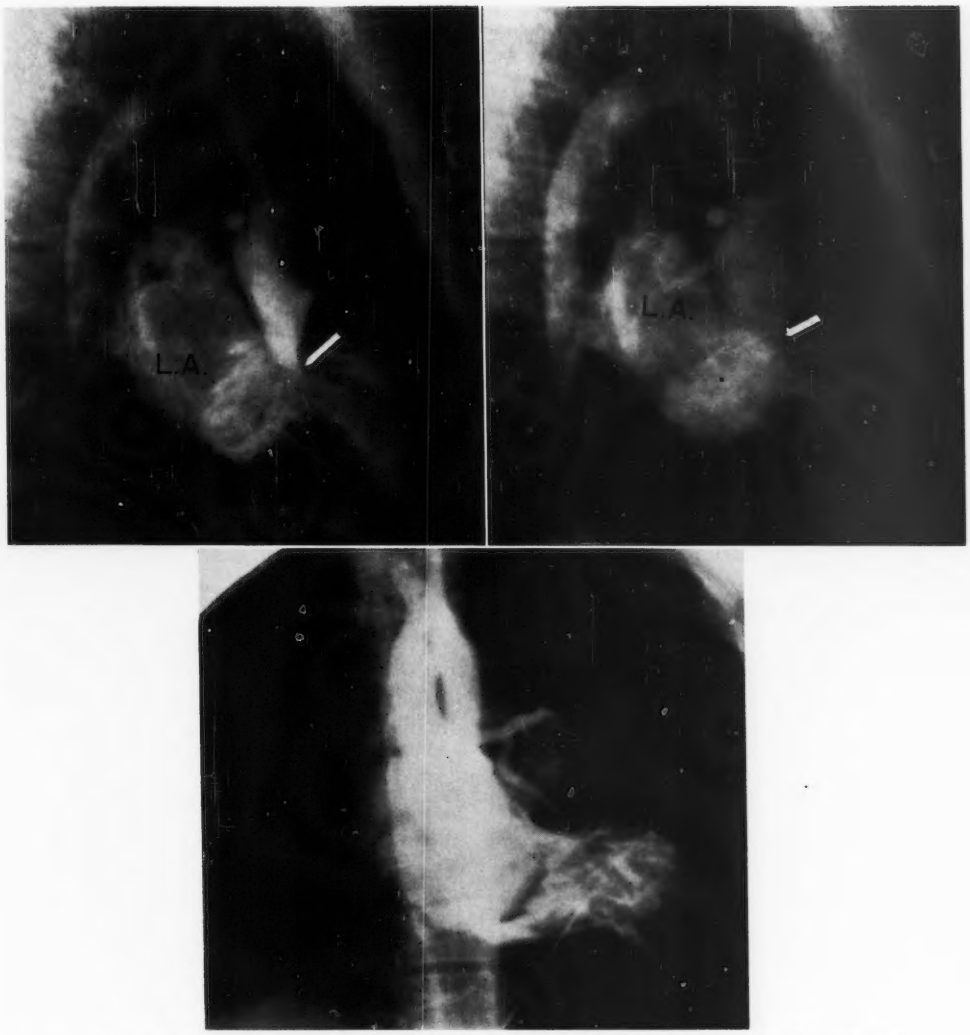

FIG. 8. Selective angiocardiogram with left ventricular injection in patient C.G. Lateral views in systole (*top left*) and diastole (*top right*). The left atrium (*LA*) is filled. *Arrow*, narrowed outflow tract. In the AP projection (*bottom*) the outflow tract is obscured by the left atrium but enlarged coronary arteries and normal aorta are demonstrated. The extreme thickness of the left ventricular wall can be appreciated.

and functional aortic stenosis in our first 2 patients. The etiology of the ventricular hypertrophy in these patients remains obscure. There was no gross evidence of endocardial fibroelastosis and the myocardium appeared normal in color and consistency. Although both patients had mitral regurgitation it would seem unlikely that this lesion could have produced severe ventricular changes with the left atrial pressure pulse remaining normal in contour. Until complete pathologic study of these hearts is carried out, we must attach to them the well-worn label of "idiopathic left ventricular hypertrophy." In the

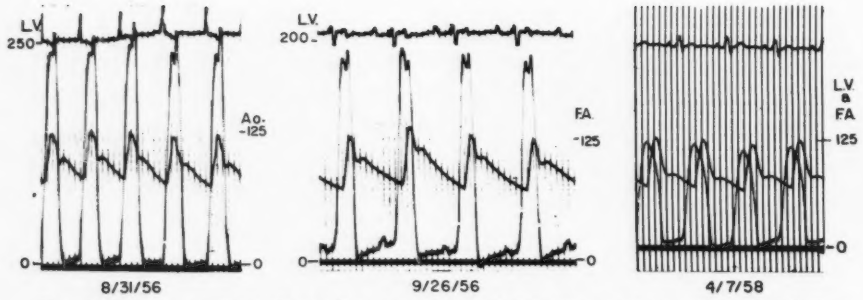

FIG. 9. Pressure tracings obtained at transbronchial left heart catheterization just before operation (*left*), 3 weeks after operation (*center*), and 18 months after operation (*right*) in patient J.R.

recent report of Bercu et al.[13] a similar patient is described. A systolic pressure gradient of 130 mm. Hg was recorded and at open operation under hypothermia no obstruction was encountered. At autopsy this patient was found to have massive symmetrical hypertrophy of both ventricles and "most remarkable was the reduction of both ventricular cavities to mere uniform slits throughout their entire length." No cause for the ventricular hypertrophy was apparent on histologic study. If a similar process, involving both the left and right ventricles, is present in patient C.G. described above, a ready explanation is afforded for the physiologically established subvalvular stenosis in the right ventricular outflow tract (fig. 6).

The recognition of functional aortic stenosis is of considerable importance since this lesion is at present not amenable to surgical correction and an unnecessary exploration of the ventricle and valve in such a patient is hazardous indeed.[12, 13] The diagnosis may be suggested by certain features present in both the patients described herein as well as in the one reported by Bercu et al. The systolic thrill and murmur were most prominent at the apex and lower left sternal border and less apparent in the aortic area. The thrill was not transmitted to the carotid vessels. Phonocardiography in patient E.Z. revealed a loud holosystolic murmur at the apex with a softer ejection murmur at the base of the heart. C.G. on the other hand had a typical ejection murmur only. In none of the patients was poststenotic dilatation of the aorta demonstrable. This latter finding is in contrast to that in patients proved to have the more usual form of congenital subvalvular aortic stenosis.[3]

In both patients at left heart catheterization the obstruction was demonstrated to lie beneath the aortic valve, as in Brock's patients with functional obstruction secondary to hypertension.[12] Thus it would seem that the diagnosis of functional aortic stenosis can be excluded by the demonstration of a pressure difference across the valve and must be suspected when the site of stenosis is shown to be below it. For this reason complete left heart and aortic catheterization would seem preferable to simple ventricular puncture in the study of patients with aortic stenosis. It is probable that selective left ventricular angiography will prove the most definitive diagnostic technic in distinguishing this lesion from the other forms of aortic stenosis and will also reveal any accompanyng mitral insufficiency.

The persistence of a large pressure gradient following the complete relief of a localized subvalvular obstruction in patient J.R. can only be attributed to functional aortic stenosis, the hemodynamic effects of which disappeared during the 19 months after operation. This would indicate that the results of late postoperative studies may be of greatest value in the assessment of operative results.

SUMMARY

Three patients are described in whom functional obstruction to left ventricular outflow was present. In 2 a significant pressure gra-

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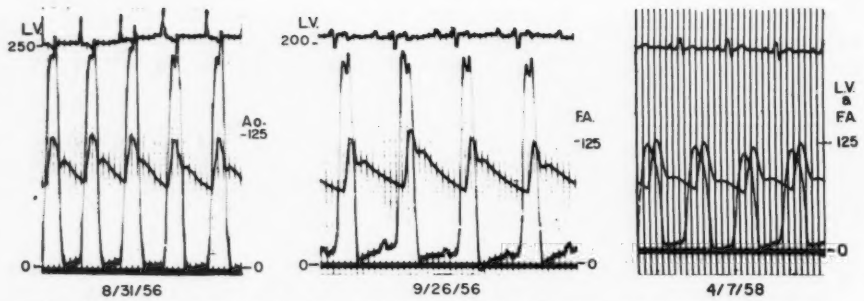

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Circulatory Changes in Acute Glomerulonephritis

By VALENTINO DEFAZIO, M.D., RAYMOND C. CHRISTENSEN, M.D., TIMOTHY J. REGAN, M.D., LESEM J. BAER, M.D., YOSHIKAZU MORITA, M.D., AND HARPER K. HELLEMS, M.D.

Conflicting opinions have been expressed as to the mechanism of pulmonary and peripheral congestion frequently observed in the oliguric stage of acute glomerulonephritis. Hemodynamic studies in 7 patients studied during the oliguric edematous phase of the disease demonstrated that these patients have high ventricular filling pressures associated with an increase in cardiac output and are, therefore, examples of a high output congestive state.

DYSPNEA, orthopnea, pulmonary rales, cardiac enlargement, gallop rhythm, and elevated venous pressures are frequently observed in acute glomerulonephritis. The symptoms of circulatory congestion in this condition are considered expressive of heart failure by the majority of authors, who consider that heart failure is a frequent complication of acute glomerulonephritis and the most frequent cause of death in the initial stage of this disease.[1-7]

Conflicting opinions have been expressed by the different investigators as to mechanism producing circulatory congestion in acute glomerulonephritis. Various explanations have been advanced, but the factors that have received major consideration as responsible for the circulatory complications are hypertension, myocardial damage, and hypervolemia.

An elevation of both systolic and diastolic blood pressure is usually present in acute glomerulonephritis, although it is frequently of moderate degree. It is generally believed to be due to an increase in total peripheral vascular resistance, but the evidence in favor of this explanation is not definite. Hypertension has been considered as the cause of "heart failure" in acute glomerulonephritis.[8-10] However, some studies have shown a poor correlation between high blood pressure and signs of circulatory congestion.[6, 11, 14] Moreover, cases of acute glomerulonephritis with cardiac enlargement without hypertension have been reported.[1, 13] Thus, the results of previous investigation indicate that hypertension may contribute to the production of circulatory congestion in acute glomerulonephritis, but that it is not the sole, and probably not the major factor.

Histologic changes in the myocardium of patients dying of acute glomerulonephritis have been observed,[1, 15, 16] whereas, others have found no significant lesions.[6, 17] According to the majority of the investigators it would be difficult to explain the circulatory derangement observed in acute glomerulonephritis solely on the basis of the reported pathologic changes in the myocardium.[18, 19]

It has been suggested that water retention, which is known to occur in acute glomerulonephritis, is the main factor producing circulatory congestion in this disease. Lyons, Jacobson, and Avery[20] showed that the administration of salt and water to normal subjects led to increase in weight, increased blood volume and elevation of the venous

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pressure. It is also known that desoxycorticosterone acetate (DOCA) may produce cardiac enlargement, pulmonary congestion, increased venous pressure, and edema, and, more recently, the same effects have been observed as a result of the sodium retention induced by cortisone.[21]

On the basis of these observations and because in 5 patients both cardiac output and arm-to-tongue circulation time were found to be normal, Davies[11] suggested that what has been called "heart failure" in acute glomerulonephritis is, in reality, a state of circulatory congestion due to hydremia. Also, Eichna and his associates[22] expressed the view that the syndrome suggesting heart failure seen in acute glomerulonephritis is not a true heart failure, but an "extracardiac circulatory congestion due to water and salt retention."

An increase of the blood volume with decreased hematocrit value has been shown to occur in acute glomerulonephritis by Cardozo[23] and by Roscoe.[14] More recently, Eisenberg[24] in 8 patients with acute glomerulonephritis, edema, venous hypertension, and cardiac enlargement has found a mean increase of the blood volume of 29 per cent with selective increase in plasma volume.

It is apparent that any attempt to evaluate the mechanism responsible for the circulatory congestion in acute glomerulonephritis requires a knowledge of the actual hemodynamic changes in these patients. Hemodynamic data in 5 patients with acute glomerulonephritis have been reported by Eichna and Farber,[25] and Davies[11] has reported hemodynamic studies in 5 patients, 4 of whom were normotensive at the time of the study. Both groups reported normal cardiac output and stroke volume. Data were not given relating left ventricular filling pressures, nor to pressures in the pulmonary circulation. It was considered, therefore, that a more detailed hemodynamic study of a group of patients in the early phase of acute glomerulonephritis would provide additional information pertaining to the actual changes of the various circulatory parameters in this disease.

Patient Material

Hemodynamic studies were carried out in 7 patients with typical clinical and laboratory findings of acute glomerulonephritis. The patient material was obtained with as little selection as possible, i.e., attempts were made to study all patients with acute glomerulonephritis admitted in the oliguric phase of the disease. Patients below the age of 10 years, however, and occasional adults who were too severely ill to cooperate were not studied. Also excluded, were those patients in whom the diagnosis was made after the diuresis had started.

The main clinical and laboratory findings of the 7 patients studied are shown in tables 1 and 2. There were 6 males and 1 female, ranging in age from 11 to 36 years; only 1 patient was under the age of 20.

Six of the 7 patients had edema, and, during the later course of their hospitalization, showed a loss of body weight, ranging from 19 to 36 pounds, as a result of diuresis. All patients were moderately to severely hypertensive. Three subjects had dyspnea, pulmonary basilar rales, slight to moderate cardiac enlargement on x-ray, and increased venous pressures; 2 of these also had orthopnea and an apical protodiastolic gallop. A fourth patient had slight cardiac enlargement, apical gallop rhythm, and increased venous pressure, but no pulmonary rales, nor did he complain of dyspnea.

All patients had urinary findings of proteinuria, hematuria, and cylindruria. The serum antistreptolysin titer was greater than 240 Todd units in 5 subjects. The blood urea nitrogen was slightly to moderately elevated in 3, the highest level being 55 mg. per 100 ml. in patient B.L. The total serum proteins were normal in all patients and the albumin ranged from 3.5 to 4.8 Gm. per cent. Plasma sodium was within normal limits in the 6 individuals in whom it was determined, plasma potassium being slightly elevated in 2.

Four of the patients had a history of "cold" or "sore throat" 2 to 3 weeks prior to admission to the hospital. In all subjects, the signs and symptoms of acute glomerulonephritis were of less than 2 weeks' duration, and they were all afebrile at the time of study.

Methods

The hemodynamic studies were carried out in the postabsorptive state. In order to decrease the apprehension and obtain a reasonably basal state, all patients were sedated with pentobarbital (Nembutal), 100 mg., or meperidine (Demerol), 50 to 100 mg., administered ½ hour before beginning the procedure.

Cardiac catheterization was carried out in the usual manner, with a double-lumen cardiac cathe-

TABLE 1.—*Clinical Findings**

Patient, sex, age (yrs.)	Dyspnea	Orthopnea	Rales	Edema	Weight change in pounds†	Heart enlargement‡	Murmurs	Gallop rhythm	Blood pressure (mm. Hg)	Venous pressure (mm. H_2O)	Circulation time (sec.)
A.B., male, 11	0	0	0	+	122 ↓ 102	Doubtful	Gr. I syst. apex	No	150/101	140	8
I.P., male, 23	0	0	0	++	205 ↓ 181	+	Gr. I syst. apex	Yes	237/158	180	15
R.T., male, 36	++	0	+	+++	195 ↓ 176	+	0	No	182/142	220	15
A.W., female, 26	0	0	0	++	139 ↓ 121	0	0	No	177/113	102	9
B.L., male, 20	+++	++	++	++	240 ↓ 210	++	0	Yes	176/126	120	13
W.H., male, 31	0	0	0	0	145 ↓ 145	0	0	0	228/128	—	—
G.J., male, 29	+++	++	+++	++++	164 ↓ 128	++	Gr. II syst. apex	Yes	190/120	140	10

*Most of the clinical findings are graded on a scale of + to ++++.

†Weight change during period of hospitalization.

‡In all cases, clinical evaluation of the heart size has been confirmed by x-ray.

ter. The distal lumen of the catheter was wedged into a branch of the pulmonary artery to record the pulmonary "capillary" pressure.[26] The proximal lumen was in the pulmonary artery. An indwelling Cournand needle was placed in the brachial artery. The cardiac output was measured by the Fick principle. Expired air was collected in a Tissot spirometer for 3 minutes, blood samples being drawn simultaneously and at a constant rate from the pulmonary artery and the brachial artery during the second minute of air collection. In 1 case, the hemodynamic response to exercise was also studied. The patient was required to pedal a bicycle ergometer in the recumbent position at the rate of 50 to 60 revolutions per minute for 4 minutes. Expired air was collected between the third and fourth minute of exercise, blood samples being drawn simultaneously and at a constant rate from the pulmonary and the brachial artery over the entire minute. Pulmonary "capillary," pulmonary artery and brachial artery pressures were measured at rest and at each minute over the 4 minutes of exercise.

Sanborn electromanometers were used for recording pressures, the zero level being 10 cm. anterior to the back. Mean pressures were obtained by electrical integration. Oxygen consumption was determined by analysis of expired air and room air for oxygen on a Pauling oxygen analyzer. A correction factor of 1.007 was used for the conversion of expired into inspired air volume.[27] Blood samples were analyzed in duplicate for oxygen content by the method of Van Slyke and Neill,[28] duplicates being required to check within 0.1 volumes per cent. The following calculations were made:

$$\text{Total peripheral resistance in dynes sec. cm.}^{-5} = \frac{BAm \times 1332}{CO}$$

$$\text{Pulmonary arteriolar resistance in dynes sec. cm.}^{-5} = \frac{(PAm - \text{“}PC\text{”}m) \times 1332}{CO}$$

$$\text{Left ventricular work index in Kg. M./min./M.}^2\ \text{BSA} = \frac{CI \times 1.055 \times (BAm - \text{“}PC\text{”}m) \times 13.6}{1000}$$

TABLE 2.—*Laboratory Findings*

Patient	Urine: Protein	Urine: Red blood cells	Urine: Casts	Blood, urea nitrogen (mg./100 ml.)	Serum proteins (Gm./100 ml.): Total	Serum proteins (Gm./100 ml.): Albumin	Serum proteins (Gm./100 ml.): Globulin	Plasma sodium (mEq./L.)	Plasma potassium (mEq./L.)	Serum antistreptolysin titer (Todd units)
A.B.	++	++++	++	38	8.3	3.8	4.5	137	5.8	>640
I.P.	++	+	+	17	8.4	4.3	4.1	140	4.2	160
R.T.	+++	++++	+++	17	7.0	3.5	3.5	140	3.8	>640
A.W.	++++	++++	++	19	7.5	4.8	2.7	149	3.9	480
B.L.	++++	++++	+	55	8.2	4.8	3.4	150	6.1	>640
W.H.	+++	+++	0	11	7.6	4.3	3.3			>625
G.J.	++++	+++	+++	36	7.4	3.9	3.5	149	4.8	240

$$\text{Left ventricular stroke work index in Gm. M./beat/M.}^2\text{ BSA} = \frac{\textit{Left ventricular work index}}{\textit{heart rate}} \times 1000$$

$$\text{Right ventricular work index in Kg. M./min./M.}^2\text{ BSA} = \frac{CI \times 1.055 \times (PAm - RAm) \times 13.6}{1000}$$

$$\text{Right ventricular stroke work index in Gm. M./beat/M.}^2\text{ BSA} = \frac{\textit{Right ventricular work index}}{\textit{heart rate}} \times 1000$$

Where: BAm = mean brachial artery pressure in mm. Hg; PAm = mean pulmonary artery pressure in mm. Hg; *"PC"m* = mean pulmonary "capillary" pressure in mm. Hg; RAm = mean right atrial pressure in mm. Hg; CO = cardiac output in ml. per second; CI = cardiac index in L. per minute per M.^{2} of body surface area; BSA = body surface area; 1332 = factor to convert mm. Hg to dynes per cm.^{2}; 1.055 = specific gravity of blood; 13.6 = specific gravity of Hg.

For statistical evaluation, the data obtained in this group of patients have been compared with those obtained in normal subjects studied in our laboratory. The normal mean values for oxygen consumption, arteriovenous oxygen difference, cardiac output and index, brachial artery pressure and total peripheral resistance have been calculated from the findings in a group of 19 normal controls. The remaining normal mean values have been obtained in a group of 6 normal subjects. For each hemodynamic parameter, the significance of the difference between the normal mean and the mean obtained in the patients with glomerulonephritis, has been evaluated by the t test.

RESULTS

The main hemodynamic data, together with their mean values, standard deviations and standard errors are shown in table 3. The same table shows the mean normal figures and the p values of the differences between the means.

The oxygen consumption was higher than normal in 3 patients, being within normal limits in the remaining 4 cases. The slight to moderate increase observed in the 3 patients could have been due to apprehension, or the increased work of breathing incident to pulmonary congestion. The mean oxygen consumption for the group of patients was 176.4 ±17.4 ml. per minute per M.^{2} BSA, as compared to the normal mean of 139 ± 6.9. The difference between the 2 means is of questionable significance, the p value being greater than 0.05 but smaller than 0.1.

The arteriovenous oxygen difference ranged from 25.7 to 45.8 ml. per L., with a mean of 33.7 ± 2.7, as compared to the normal mean of 39.8 ± 1.86. The difference between these 2 means is of questionable significance ($p > 0.05$).

The cardiac output was significantly increased in all patients, as shown by a cardiac index ranging from 4.43 to 7.08 L. per minute per M.^{2} BSA. The mean for the group was 5.3 ± 0.36, which, compared with the normal

TABLE 3.—*Hemodynamic Data*

Patient, sex, age (yr.)	Body surface area ($M.^2$)	Oxygen consumption (ml./min./$M.^2$ BSA)	Oxygen A-V difference (ml./L.)	Cardiac output (L./min.)	Cardiac index (L./min./$M.^2$ PSA)	Heart rate	Stroke volume index (ml./beat/$M.^2$ BSA)	Arterial oxygen saturation (%)	Pressures (mm. Hg)					Total peripheral resistance (dynes sec. $cm.^{-5}$)	Pulmonary arteriolar resistance (dynes sec. $cm.^{-5}$)	Left ventricular work index (Kg. M./min./$M.^2$)	Left ventricular stroke work index (Gm. M./beat/$M.^2$)	Right ventricular work index (Kg. M./min./$M.^2$)	Right ventricular stroke work index (Gm. M./beat/$M.^2$)
									Bronchial artery mean	Pulmonary capillary	Pulmonary artery (mean)	Right atrium (mean)							
A.B., male, 11	1.45	176	25.7	10.27	7.08	105	67.4	91	136	15	22	7		1116	171	12.28	117	1.54	15
I.P., male, 23	2.13	159	31.7	10.66	5.00	70	71.5	92	182	24	27	11		1370	23	11.36	162	1.18	15
R.T., male, 36	2.02	140	31.7	8.96	4.43	65	68.2	93	142	24	32	11		1261	71	7.52	113	1.66	20
A.W., female, 26	1.53	143	29.4	7.45	4.87	73	66.6	95	140	23	31	14		1502	86	8.18	112	1.18	16
B.L., male, 20	2.16	193	42.5	9.85	4.56	56	81.4	87	140	39	50	15		1110	89	6.55	117	2.28	41
W.H, male, 31	1.73	152	29.7	8.86	5.12	88	58.2	94	163	14	21	5		1470	63	10.95	124	1.17	14
G.J., male, 29	1.83	272	45.0	10.00	5.46	83	65.8	96	166	30	47	12		1330	136	11.76	142	2.73	33
Mean		176.4	33.7		5.30	77	68.4		153	24	32.7	10.3		1308	90.1	9.80	127	1.68	21
Standard deviation		46.1	7.2		0.94		7.6		21	8.6	11.3	3.6		45	47.0	1.93	18.7	0.61	10.6
Standard error		17.4	2.7		+0.36		2.8		7.9	3.3	4.3	1.4		17.3	18	0.78	7.3	0.23	4.0
Normal mean		139	39.8		3.55		42.5		91.9	6	14	5		1305	114	4.03	50	0.40	5
± S.E.		±6.9	±1.9		±0.17		±3.8		±2.6	±0.3	±1.5	±0.8		±29.1	±25	±0.45	±4.8	±0.08	±0.49
p		<0.1	<0.1		<0.01		<0.001		<0.001	<0.001	>0.001	0.05		>0.1	<0.001	<0.001	0.001	0.01	0.01
		>0.03	>0.05								<0.01								

mean of 3.55 ± 0.17, appears markedly elevated. The difference is significant at a level of less than 1 per cent (fig. 1). Although cardiac output tended to be higher in those patients with an elevated oxygen consumption, there was no significant correlation between these 2 parameters.

The heart rate was within normal limits in 6 of the 7 patients, being 105 in patient A.B. The stroke volume was significantly greater than normal in all patients, the mean stroke volume index for the group being 68.4 ± 2.8 ml. per beat per M.² BSA, as compared to the normal of 42.5 ± 3.8.

The arterial oxygen saturation was within limits normal for our laboratory in 6 patients. One patient (B.L.) had an arterial oxygen saturation of 87 per cent. This patient had marked pulmonary congestion with dyspnea, orthopnea, and pulmonary rales. Both pulmonary congestion and alveolar transudation can explain the low oxygen saturation of the arterial blood observed in this patient.

The hemoglobin values ranged from 9.8 to 13.1 Gm. per 100 ml. These levels are probably falsely low as a consequence of hemodilution due to the water retention that is observed in acute glomerulonephritis.[14, 23, 24] These hemoglobin values, however, are all within a range that is usually not accompanied by any significant hemodynamic change.

The pulmonary "capillary" pressure was significantly elevated in all patients, ranging from 14 to 39 mm. Hg with a mean of 24.0 ± 3.3, as compared to the normal mean of 6 ± 0.3. The difference is significant at the level of less than 1 per cent. This marked increase in pulmonary "capillary" pressure, in the absence of mitral disease or pulmonary vein obstruction, indicates an elevated left ventricular filling pressure (fig. 2).

A satisfactory right ventricular pressure curve was obtained in 4 of the 7 patients. In these 4 cases, the right ventricular end-diastolic pressures were very close to the mean right atrial pressure, the differences being not greater than 1 mm. Hg. It was decided, therefore, to use the mean right atrial pressures, which were obtained in all 7 patients, as an index of the right ventricular filling pressures. Some objections have been raised to the use of the mean right atrial pressure as reflecting the right ventricular end-diastolic pressure.[29] However, Sarnoff[30] observed in the experimental animal that the correlation between these two pressures is satisfactory in the low and medium ranges. For this and other technical reasons, Sarnoff[30] preferred to use mean atrial pressures instead of directly recorded ventricular end-diastolic pressures. In our study, the mean right atrial pressure was elevated in 4 of the 7 patients, ranging from 5 to 15 mm. Hg, with a mean of 10.3 ± 1.4, as compared to the normal of 5.0 ± 0.8. As

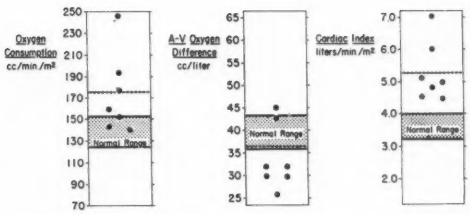

FIG. 1. Range of oxygen consumption, arteriovenous oxygen difference, and cardiac index in normal subjects and patients with acute glomerulonephritis. *Closed circles*, individual patients; *dotted line*, mean of the patient series; *shaded areas*, 2 times the standard error of the mean for the normal subjects.

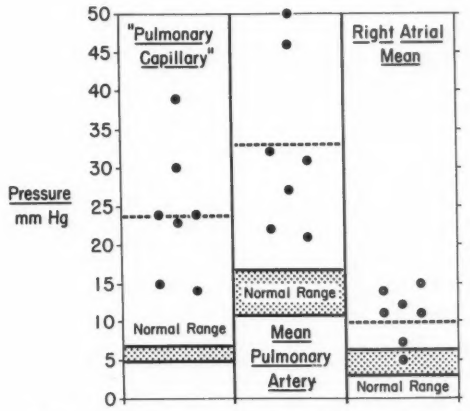

FIG. 2. Comparison of intravascular pressures in normal subjects and patients with acute glomerulonephritis. Symbols as in figure 1.

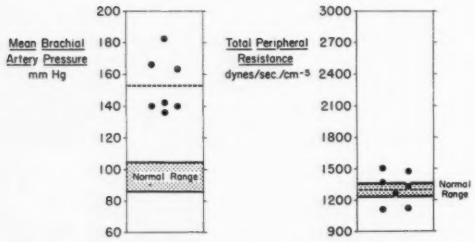

FIG. 3. Brachial artery pressure and peripheral arterial resistance in normal subjects and patients with acute glomerulonephritis. Symbols as in figure 1.

tricuspid valvular disease was absent in these patients, the elevation of the mean right atrial pressure was considered to be an indication of elevated right ventricular filling pressure.

A marked elevation of both systolic and diastolic pressures in the systemic circulation was present in all patients. The brachial artery mean pressure ranged from 136 to 182 mm. Hg with a mean of 153 ± 7.9. The calculated total peripheral resistance was within normal limits in all cases, however, ranging from 1,116 to 1,502 dynes sec. cm.$^{-5}$, with a mean of 1,308 ± 17.3, as compared to the normal mean of 1,305 ± 29.1 (fig. 3).

The mean pulmonary artery pressures ranged from 21 to 50 mm. Hg, with a mean of 32 ± 4.3, which is significantly higher than the normal mean of 14 ± 1.5. The pulmonary arteriolar resistance was within normal limits in all patients (fig. 2).

Both left and right ventricular total and stroke work against pressure were markedly increased, the difference from the normal values being statistically significant at the level of 0.001 for the left ventricle and of 0.01 for the right ventricle (fig. 4).

DISCUSSION

The 7 patients with acute glomerulonephritis were characterized from a hemodynamic standpoint by a high cardiac output and stroke volume, a normal to low arteriovenous oxygen difference, an elevated left ventricular filling pressure, a normal total peripheral resistance, an elevated pulmonary artery pressure, and a normal pulmonary arteriolar resistance. In 5 of these subjects, an increase of the right ventricular filling pressure was also present. Both total and stroke work of the right and left ventricles were markedly elevated in all patients.

The high cardiac output places these patients in the group of the high output states, such as is seen in normal subjects during exercise or under emotional stress, and in patients with such conditions as marked anemia, hypoxemia, hyperthyroidism, arteriovenous fistula, and beri-beri. None of these disease entities associated with high output was present in these patients. The slight increase in the mean oxygen consumption for the group was of questionable statistical significance and does not explain the moderate to marked increase in cardiac output. In fact, an elevation of the cardiac output was also present in the 4 subjects in whom the oxygen consumption was within normal limits. In none of the patients was the hemoglobin low enough to increase the cardiac output significantly. Only 1 patient had a slight decrease of the arterial oxygen saturation, thus the increase in output cannot be explained on the basis of hypoxemia.

Hypertension and myocardial damage, both of which have been suggested as possible causes of the circulatory changes in acute glomerulonephritis, do not produce, per se, an increase of the minute volume output of the heart. On the other hand, hypervolemia could explain the high cardiac output observed in this group of patients. Hypervolemia in the oliguric phase of acute glomerulonephritis has been reported.[14, 23, 24] More extensive studies are necessary, however, to determine whether a significant correlation exists between hypervolemia and minute volume output of the heart.

The left ventricular filling pressure was elevated in all 7 patients, with consequent increase in pulmonary venous and capillary pressures, which, in some of the patients, reached levels sufficiently high to produce symptoms and signs of pulmonary congestion. This elevation of the left ventricular filling pressures might be interpreted as evidence that the patients were in left ventricular

failure. The same applies to the right ventricle in the 5 cases that showed an increase in the filling pressure of this chamber. However, the concept that an elevation of the ventricular end-diastolic pressure always indicates heart failure is open to question.

Patterson and Starling,[31] in the heart-lung preparation, observed that increments in ventricular filling pressure, within certain limits, were accompanied by a greater energy of contraction with an increase in cardiac output and stroke work. A better correlation existed between length of the myocardial fibers and force of contraction. Thus, what is now known as the Starling law of the heart relates stroke work to diastolic volume and not to diastolic pressure.

Because of the difficulty in measuring end-diastolic volume, Sarnoff and his associates[30] tried to correlate ventricular filling pressure and stroke work in the experimental animal, both with the open and the closed chest. They found a good correlation between these 2 parameters, but for each heart, instead of 1 curve, they found a family of pressure-work curves. A shift from one curve to another was produced by a "modification of factors which govern the response of the myocardium" or "the vascular resistance."

Although the Starling mechanism is not the sole factor regulating the heart's performance in the intact animal, from the above-mentioned observations it appears likely that a normal heart may respond to an increase in inflow volume with an increase in end-diastolic pressure. In the light of this concept, the increased ventricular filling pressures in our patients would not necessarily indicate heart failure. A state of failure would have been demonstrated if, on exercise, a subnormal response in cardiac output and work had occurred. Because of the clinical condition of the patients, only one was studied during exercise. In this patient the total circulatory response to exercise could not be considered abnormal. In the absence of exercise studies in the remaining 6 patients, it would be difficult to determine whether some, or all, of them were in heart failure.

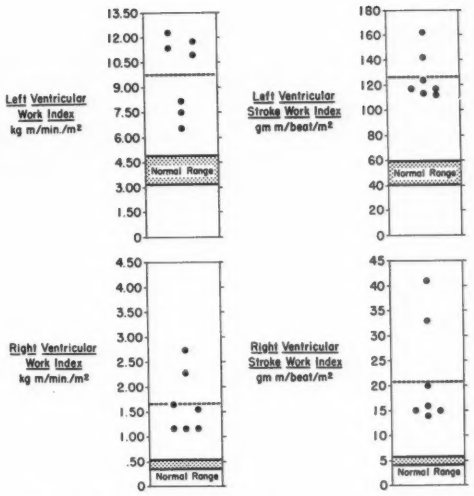

FIG. 4. Right and left ventricular work parameters in acute glomerulonephritis compared to normal subjects. Symbols as in figure 1.

The presence of a normal calculated peripheral resistance distinguishes these patients with acute glomerulonephritis from other high output states in which decrease in peripheral resistance is usually observed and the high cardiac output is not associated with an increase in arterial blood pressure. This difference would indicate that the compensatory vasodilatation, which is ordinarily present in other high output states, is absent in patients with acute glomerulonephritis. In these patients, the combination of a greater inflow volume with an elevated arterial blood pressure, produces an elevation of the left ventricular work load far above that present in comparable high output states in which the mean arterial blood pressure is normal. According to the Starling concept, one could postulate that this marked increase in work load requires a greater diastolic volume and, in turn, a significant elevation of the filling pressure.

SUMMARY

Hemodynamic studies employing the technic of cardiac catheterization have been carried out in 7 patients with typical clinical and laboratory findings of acute glomerulonephritis in the oliguric phase. All patients were hypertensive, 6 were edematous; 3 had car-

diac enlargement, gallop rhythm, and signs of pulmonary congestion. The arm-to-tongue circulation time was measured in 6 patients and was normal.

The main hemodynamic findings observed in all patients were as follows: high cardiac output and stroke volume, normal to low arteriovenous oxygen difference, elevated left ventricular filling pressure, normal total peripheral arteriolar resistance, elevated pulmonary artery pressure, and normal pulmonary arteriolar resistance. An increase of the right ventricular filling pressure was present in 5 patients. Both total and stroke work of the right and left ventricles were markedly elevated in all patients.

The high cardiac output observed in this group of patients could not be explained on the basis of anemia, hypoxemia, or increased oxygen consumption. Water retention and the consequent hypervolemia known to occur in acute glomerulonephritis could explain the elevation of the cardiac output.

The finding of a normal total peripheral resistance would indicate absence of the vasodilatation that usually accompanies other high output states.

The elevation of the ventricular filling pressures might be interpreted as evidence that all patients were in heart failure. According to the Starling concept, however, an elevated ventricular filling pressure is not necessarily indicative of heart failure. The combination of hypertension with increased inflow volume in this group of patients produced an elevation of the left ventricular work load far above that present in other high output states of comparable degree, in which the mean arterial pressure is not increased. It is suggested that the resulting increase in work load was of such a magnitude as to require a greater diastolic volume and, in turn, a significant elevation of the filling pressure.

The circulatory response to exercise would show whether the heart in some of the patients with acute glomerulonephritis is in failure. In the only patient studied during exercise, the circulatory response could not be considered abnormal. Further studies in this line are needed.

Acknowledgment

We wish to express our appreciation to the following technicians who at one time or another aided in this work: Miss Mary Richards, Miss Virginia Everett, and Miss Carolyn Maleyko; and to Mrs. Shirley Loy for secretarial services.

Summario in Interlingua

Studios hemodynamic per medio del technica de catheterisation cardiac esseva effectuate in 7 patientes con typic constatationes clinic e laboratorial de glomerulonephritis acute in le phase oliguric. Omne le patientes esseva hypertensive, 6 esseva edematose, e 3 habeva allargamento cardiac, rhythmo de galopo, e signos de congestion pulmonar. In 6 patientes, le tempore del circulation inter bracio e lingua esseva measurate e trovate normal.

Le sequentes es le major constatationes hemodynamic facite in omne le patientes. Alte valores pro rendimento cardiac e volumine per pulso, normal o basse valores in le differentia arterio-venose de oxygeno, elevate valores del pression de replenation sinistro-ventricular, normal resistentia peripheric total, elevation del tension pulmono-arterial, e normal resistentia pulmono-arteriolar. Un augmento del pression de replenamento dextero-ventricular esseva presente in 5 patientes. In omne patientes, le travalio total e etiam le travalio per pulso in le ventriculos dextere e sinistre esseva marcatemente elevate.

Le alte rendimento cardiac observate in iste patientes non poteva esser explicate per anemia, hypoxemia, o augmento del consumption de oxygeno. Le retention de aqua e le consequente hypervolemia, que occurre cognoscitemente in glomerulonephritis acute, provide possibilemente un effiplication pro le elevation del rendimento cardiac.

Le constatation de un normal resistentia peripheric total pare indicar le absentia del vasodilatation que es usualmente un tracto de altere statos con augmento del rendimento cardiac.

Le elevation del pressiones de replenation ventricular es possibilemente interpretabile como prova que omne le patientes se trovava in disfallimento cardiac. Tamen, secundo le conception de Starling, un elevate pression de replenation ventricular non indica necessarimente le presentia de disfallimento cardiac. Le combination de hypertension con augmento del volumine de influxo produceva in iste gruppo de patientes un elevation del carga de labor sinistro-ventricular multo plus marcate que lo que se incontra in altere statos a augmentate rendimento de grado comparabile in le quales le tension arterial medie non se accresce. Es presentate le these que le resultante augmento del carga de labor esseva de un tal magnitude que illo necessitava un plus grande volumine diastolic e, per consequente, un elevation significative del pression de replenation.

Le responsa del circulation a exercitios physic poterea monstrar si o non le corde in certe patientes con glomerulonephritis acute se trova in stato de disfallimento. Un sol patiente esseva studiate durante exercitio. In ille, le responsa circulatori non poteva esser designate como anormal, sed studios additional in iste respecto es necessari.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Bence Jones Protein. A paper "On a new substance occurring in the Urine of a patient with Mollities Ossium" was read before the Royal Society April 22, 1847, by Henry Bence Jones (1813-1873), Physician to St. George's Hospital. This appears in the *Philosophical Transactions of the Royal Society of London* for the year 1848, part I, pp. 55-62 (vol. 138).

"On the 1st of November 1845 I received from *Dr. Watson* the following note, with a test tube containing a thick, yellow, semi-solid substance:—'The tube contains urine of very high specific gravity; when boiled it becomes highly opake; on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but, as it cools assumes the consistence and appearance which you see: heat reliquifies it. What is it?'

"A few hours afterward a specimen of the same urine, passed by a grocer forty-seven years of age, who had been out of health for thirteen months, was sent to me by *Dr. MacIntyre*. He being in attendance on the case with *Dr. Watson* had two days previously first observed the peculiar reactions of the urine.

"The specimen of urine was slightly acid; specific gravity 1034.2; it contained a sediment consisting of crystalline phosphate of lime, oxalate of lime, and cylinders of fibrin. The urine became thick with heat from a desposit of phosphates, but cleared with a drop of acid. It gave no precipitate with an excess of nitric acid, unless left to stand, or unless heated and left to cool, when it became solid. This solid redissolved by heat, and again formed on cooling. Continued boiling with strong nitric acid evolved but little gas, and did not quickly hinder this reaction. Hydrochloric acid gave the same solid precipitate, soluble by heat. Strong acetic acid gave only a slight precipitate, which redissolved by heat. Caustic potash and sulphate of copper gave a splendid bright blue, clear liquid, passing over when heated to claret colour. . . .

"January 2nd. The patient died. The following day I saw that the bony structure of the ribs was cut with the greatest ease, and the bodies of the vertebrae were capable of being sliced off with the knife. For an account of the structure of the bone, see a paper by *Mr. Dalrymple* in the third number of the Dublin Journal, August 1846. . . .

"The ultimate analysis of this substance may be represented by C_{48}, H_{38}, N_6, O_{18}, or by C_{40}, H_{31}, N_5, O_{15}; according as protein is=C_{48}, H_{37}, N_6, O_{15}, or C_{40}, H_{30}, N_5, O_{12}. . . . Hence it is an oxide of albumen, and from ultimate analysis, it is the hydrated deutoxide of albumen. . . .

"The peculiar characteristic of this hydrated deutoxide of alubumen was its solubility in boiling water, and the precipitate with nitric acid being dissolved by heat and reformed when cold. . . .

"This substance must again be looked for in acute cases of mollities ossium. The reddening of the urine on the addition of nitric acid might perhaps lead to the rediscovery of it. . . ."

Right Bundle-Branch Block

A Vectorcardiographic and Electrocardiographic Study of Ventricular Septal Defect Following Open-Heart Surgery

By JANET DICKENS, M.D., VLADIR MARANHAO, M.D., AND HARRY GOLDBERG, M.D.

Confusion still exists regarding the differentiation between right bundle-branch block and right ventricular hypertrophy. Study of patients after open-heart surgery was helpful in this problem because postoperative changes in electrocardiograms and vectorcardiograms were clearly due to traumatic disturbance of the right bundle branch and not to right ventricular hypertrophy.

THE differentiation between right bundle-branch block and right ventricular hypertrophy remains a difficult one in many instances. Many methods of investigation have been applied to this problem, including endocardial electrocardiography[1-4] and vectorcardiography.[5, 6] Proponents of the latter technic have suggested that the differentiation can be made from characteristic loop appearances. An opportunity was provided to examine this proposal in patients who underwent open-heart surgery for ventricular septal defect and ventricular septal defect with pulmonic stenosis and in whom traumatic right bundle-branch block was produced.

MATERIAL AND METHODS

Seven patients ranging in age from 2 to 32 years who underwent open-heart surgery constitute the present series. Five had repair of an isolated ventricular septal defect and 2 had pulmonic stenosis in addition. The defect was situated in the membranous septum in all but 1 patient. Open-heart surgery was performed with the use of the sigmamotor pump and Freidland-Gemeinhardt oxygenator.[7] In 5 patients the defect was repaired with Nylon sutures and in 2 with Ivalon sponges. The pulmonic stenosis was relieved by splitting of the commissures under direct vision, by resecting the muscular ridge, or by both procedures.

A 12-lead electrocardiogram including V_{4R} when possible was obtained before and after surgery with a polyoscillographic recorder.* The time interval between surgery and the second electrocardiogram and vectorcardiogram varied from 14 days to 1 year.

Vectorcardiograms with both the cube system of Grishman[8] and the tetrahedron system[9] were obtained before and after operation. The vector loops were recorded by a Sanborn vector system and Visoscope.*

The electrocardiographic criteria for incomplete or complete right bundle-branch block were those of Barker and Valencia,[10] Wilson and associates,[11] and Rodriguez and Sodi-Pallares.[12] Criteria for right ventricular hypertrophy were those of Sokolow and Lyon.[13] The vectorcardiograms were analyzed for right bundle-branch block and right ventricular hypertrophy according to the criteria of Grishman[14] as follows: *Right ventricular hypertrophy*—clockwise inscription of the loop in the horizontal plane; anterior and rightward position of the loop depending on the degree of hypertrophy; absence of conduction delay. *Right bundle-branch block*—counterclockwise inscription of the loop in the horizontal plane; terminal appendage directed to the right and anteriorly; conduction delay in the terminal appendage; orientation of the T loop opposite to the terminal appendage.

RESULTS

Vectorcardiograms and Electrocardiograms before and after Operation. Four patients are included in this group, 2 with isolated ventricular septal defect and 2 with associated pulmonic stenosis.

The preoperative data were variable (table 1, cases 1 to 4, and fig. 1 *Top*). In case 1 the electrocardiogram and vectorcardiogram were

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*Sanborn Company, Waltham, Mass.

TABLE 1.—*Electrocardiographic Data*

Case number*		Interval post-op	QRS pattern V_1	QRS duration V_1	Intrinsicoid deflection V_1	Height of R or R′ V_1	Duration of R′ V_1	Duration of S Lead 1	Duration of S V_6
1	Pre		rS	0.04	0.02	1.0	0.01	0.02	0
	Post	5 mos.	rsR′	0.10	0.07	8.0	0.04	0.05	0.05
2	Pre		RS	0.06	0.02	6.0	0.03	0.01	0
	Post	2 mos.	rsR′	0.12	0.04	15.0	0.08	0.08	0.08
3	Pre		RSr′	0.07	0.06	6.0	0.01	0.03	0.02
	Post	2 mos.	RSR′	0.09	0.07	11.0	0.05	0.05	0.04
4	Pre		rR′s	0.08	0.03	9.0	0.01	0.03	0.01
	Post	14 days	rSR′	0.11	0.06	26.0	0.06	0.08	0.07
5	Pre		RS	0.09	0.02	14.0	0.03	0.04	0.01
	Post	1 year	rsR′	0.15	0.12	17.0	0.09	0.12	0.09
6	Pre		R	0.05	0.04	31.0	0.04	0.04	0.01
	Post	5 mos.	rR′	0.11	0.08	15.0	0.08	0.08	0.06
7	Pre		rSr′	0.09	0.01	1.0	0.01	0	0.03
	Post	2 mos.	rSr′	0.09	0.02	2.0	0.02	0.01	0.02

*Pre, preoperative; Post, postoperative.

considered to be within normal limits. In case 2 the electrocardiogram was equivocal for right ventricular hypertrophy. The vectorcardiogram suggested this diagnosis in the tetrahedron system but appeared normal in the cube system. In case 3 an RSr′ pattern of normal duration was present in V_1. The r′ was smaller than the R in V_1, and the s wave in leads I and V_6 was of normal duration. The RSr′ pattern was thus considered to be nonspecific, but analysis of the electrocardiogram and vectorcardiogram suggested the presence of right ventricular hypertrophy. In case 4 the electrocardiogram was again problematic. An rR′s was present in V_1 of normal duration and with a normal intrinsicoid deflection. The S wave in leads I and V_6 was likewise normal in duration. The R′ was larger than the initial r, suggesting right ventricular hypertrophy.[10] In addition the electrocardiogram met the criteria of Rodriguez and Sodi-Pallares for incomplete right bundle-branch block.[12] The vectorcardiogram, however, showed the characteristics of right ventricular hypertrophy. Generally, the cube system of vectorcardiography appeared to be superior to the tetrahedron, particularly in regard to correlation between the vectorcardiographic loop and the precordial-lead configuration.

The postoperative electrocardiograms in all patients showed significant changes consistent with right bundle-branch block (table 1, cases 1 to 4, and fig. 2 *Top*). The duration of the QRS complex, the intrinsicoid deflection, and the duration of the S wave in leads I and V_6 were increased in all tracings. The morphology of the V_1 patterns changed in 2 patients. In cases 1 and 2 with an rS and an RS complex in V_1 preoperatively, an R′ of distinct magnitude appeared postoperatively. In cases 3 and 4 the r′ and R′ in V_1 present preoperatively increased in magnitude and duration postoperatively.

The vectorcardiograms likewise showed striking changes postoperatively (fig. 2 *Top*). In the horizontal plane in all cases the loops in both the cube and tetrahedron systems were directed counterclockwise, changing from the clockwise direction seen preoperatively in 3 patients. This uniformity in direction of inscription was not seen in the sagittal and frontal planes. The loops which were previously mostly anterior in position were now

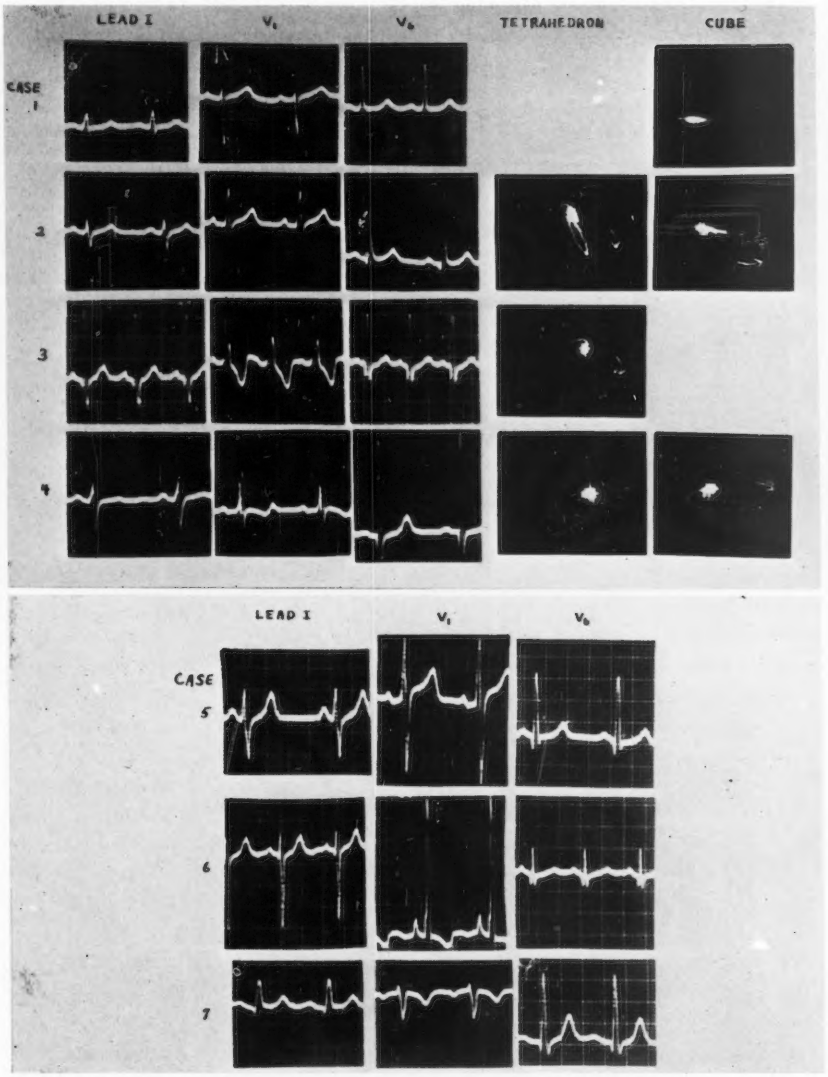

FIG. 1. *Top.* Preoperative tracings in cases 1 to 4. Only the horizontal plane vectorcardiograms are shown. The vector loops of cases 3 and 4 are indicative of right ventricular hypertrophy. The tetrahedron loop of case 2 is also consistent with right ventricular hypertrophy. *Bottom.* Preoperative electrocardiograms in cases 5 to 7. No vectorcardiograms were obtained in this group.

found to be mainly to the left in the cube system and to the left and somewhat posterior in the tetrahedron. Of particular importance was the new appearance of a terminal appendage of distinct magnitude in all cases, directed to the right and anteriorly. Conduction delay was noted in the terminal appendage in the form of crowding of the time markings and irregularity of the loop. The T loop was directed opposite to the terminal appendage.

No Preoperative Vectorcardiograms. Three patients are included in this group (table 1,

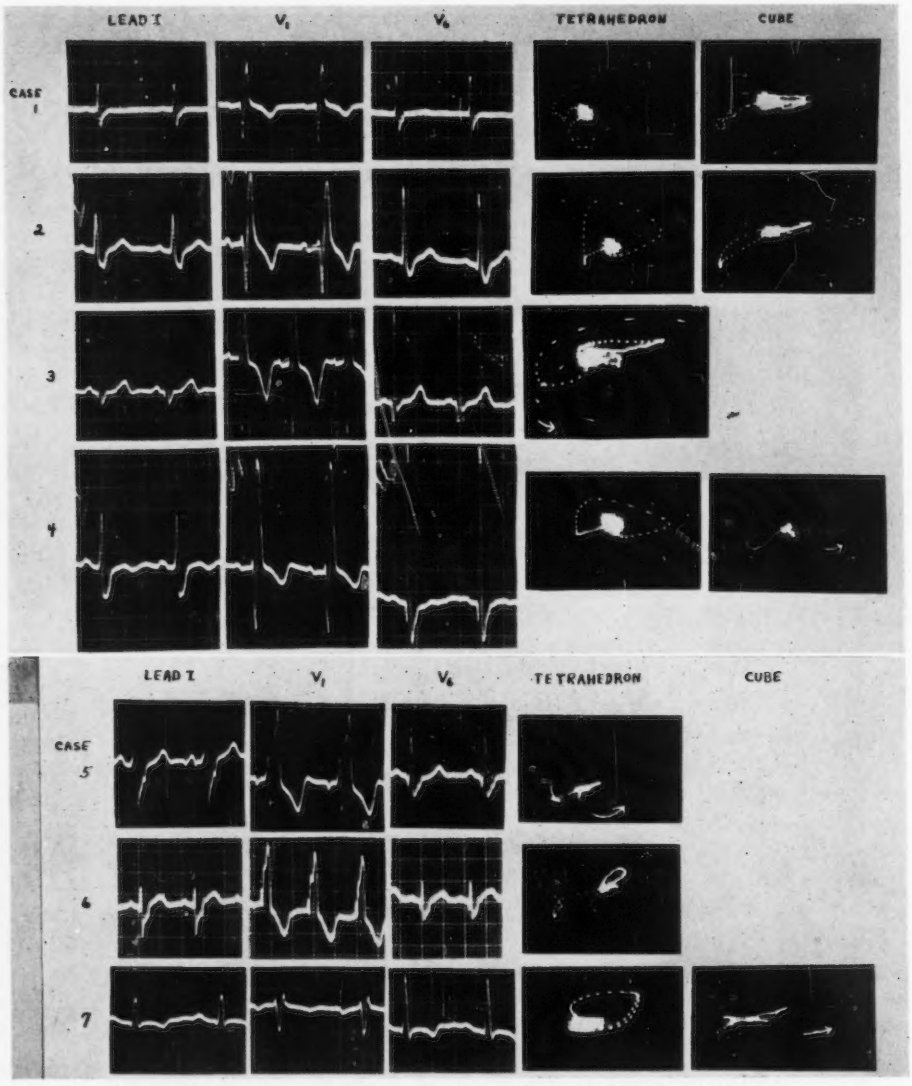

FIG. 2. *Top.* Postoperative data in cases 1 to 4. Note the similarity between the electrocardiograms and vectorcardiogram and in particular the anteriorly directed terminal appendage. Horizontal plane vectorcardiograms are shown. *Bottom.* Postoperative data in cases 5 to 7. The vectorcardiograms of cases 5 and 6 are indicative of right bundle-branch block while that of case 7 is normal. Only the horizontal plane loops are shown. Two exposures of the tetrahedron loops are present in cases 5 and 6.

cases 5 to 7, fig. 1 *Bottom*). The preoperative electrocardiogram was normal in 1 case (case 7) and consistent with right ventricular hypertrophy in 2 (cases 5 and 6). Postoperatively in the 2 latter patients right bundle-branch block was produced (table 1 and fig. 2 *Bottom*, cases 5 and 6) as noted in the electrocardiogram by the striking changes in the patterns and durations of the complexes. The postoperative vectorcardiograms showed findings simi-

lar to the previous group, that is, counterclockwise rotation of the body of the loops, and a huge terminal appendage with conduction delay directed anterior and rightward. In case 7 there was little change in the postoperative electrocardiogram. The V_1 r′ which appeared postoperatively was present in V_2 preoperatively. This finding can be explained by change in electrode positions. The postoperative vectorcardiogram showed counterclockwise direction of the loop with a very small terminal appendage without conduction delay, which was within the normal variation.

Discussion

The location of the cardiac conduction system in relation to defects of the membranous ventricular septum has been extensively investigated by Truex and Bishof.[15] The position of the common bundle of His in the posterior margin of the defect exposes it to injury by suturing during surgery. The right bundle branch may be injured in particular, because of the great variability in both the branching of the common bundle at the posteroinferior angle of the defect and in the course of the right bundle branch in the interventricular septum. The right bundle may descend either posterior or anterior to the defect and in the form of one or several fascicles. Thus, there may be injury to the right bundle, as in 1 of our cases, during repair of a defect situated in the muscular septum. In 1 case reported by Truex periarterial conduction tissue was dissected about a transposed pulmonary artery. This observation raises the question of possible injury to the conduction tissue during the performance of the pulmonary valvotomy in the cases of tetralogy of Fallot in this series. In addition to injury to the conduction tissue hemorrhage within the atrioventricular node and bundle branches was noted at postmortem examination in some cases.

On the basis of these studies the postoperative right bundle-branch block, which developed in the patients presented here, was presumed to be traumatic in origin, resulting from the inadvertent placement of sutures at surgery; indeed, the abnormal conduction was noted to occur during the operative procedure, as the sutures were being placed within the septum. This event has been noted also by other groups reporting on the repair of ventricular septal defects by open-heart surgery.[16, 17] When right bundle-branch block does not occur following surgery, as in 1 patient in our group, it can be postulated that the area of the conduction tissue was avoided during the operative procedure.

The production of right bundle-branch block was accompanied by striking changes in the electrocardiogram. The duration of the QRS complex and ventricular activation time was markedly increased. An RSR′ pattern appeared in those patients in whom it was not present preoperatively and became more significant in those in whom it was noted before surgery. Of greater importance was the increase in duration of the R′ in V_1 and the S wave in leads I and V_6. The latter findings appear to be much more significant than the morphology of the QRS complex alone.

The origin and interpretation of the RSR′ patterns has long been a subject of contention. It can be said however, that in the presence of an RSR′ complex the differentiation between right ventricular hypertrophy and right bundle-branch block often cannot be made electrocardiographically. In particular, in the presence of an RSR′ complex of normal duration and with a normal intrinsicoid deflection, the differentiation between incomplete right bundle-branch block and a normal variant may be impossible. Although some investigators[12] attribute the presence of 2 positive deflections (R and R′) exclusively to right bundle-branch block, it has been demonstrated by endocardial electrocardiography[2] that an RSR′ pattern can be recorded from the right ventricle of patients with right ventricular hypertrophy or right bundle-branch block and from normal persons. Grisham and associates[5, 18] also obtained 2 different vectorcardiographic loops in patients with similar RSR′ patterns in V_1. Criteria were then proposed by these workers

for the vectorcardiographic diagnosis and differentiation of right ventricular hypertrophy and right bundle-branch block. Since the diagnosis of right bundle-branch block could be confirmed in the present group of patients, an ideal situation was presented to evaluate these proposed criteria. The results obtained support the differentiation between these entities by vectorcardiography.

The vectorcardiograms of the patients who developed traumatic right bundle-branch block following surgery present the loop characteristics described by Grishman and associates and attributed by them to clinical right bundle-branch block. The postoperative changes in the vectorcardiograms were striking and uniform, particularly in the horizontal plane. Distinct reversal of the loop to a counterclockwise direction occurred in the patients in whom a clockwise direction in the horizontal plane was present preoperatively. The position of the loop likewise was markedly changed. Preoperatively the loops were mostly anterior in both systems, while postoperatively they were mainly to the left in the cube and to the left and somewhat posterior in the tetrahedron. A terminal appendage, which appeared postoperatively, corresponded with the broad R′ of V_1 and the S wave of leads I and V_6. Thus, the vectorcardiogram appeared to be superior in demonstrating the mechanism of right bundle-branch block.

In this study as in others[5, 18] the differentiation between right ventricular hypertrophy, right bundle-branch block, and a normal variant often cannot be made electrocardiographically in the presence of an RSR′ pattern in V_1. In addition, different types of vectorcardiographic loops may be recorded in the presence of similar RSR′ patterns in V_1. However, after the production of right bundle-branch block by surgery characteristic changes in the vectorcardiographic loops were recorded in all patients. This observation suggests that these specific loop characteristics, when encountered in clinical vectorcardiography, may be attributed to right bundle-branch block. In some of our patients reexamined in the early postoperative period who developed right bundle-branch block, it cannot be presumed that right ventricular hypertrophy was relieved immediately by surgery. Thus, when the clinical picture suggests that both right bundle-branch block and right ventricular hypertrophy may coexist, the vectorcardiogram appears to demonstrate the predominant lesion only.

Summary

Seven patients who underwent open-heart surgery for repair of ventricular septal defect were studied by electrocardiograms and vectorcardiograms before and after operation. Traumatic right bundle-branch block was produced by the operative procedure. In association with this abnormality in conduction, characteristic changes occurred in the vectorcardiographic loops. The vector loop features may be applied in the differentiation between right bundle-branch block and right ventricular hypertrophy in the presence of an equivocal electrocardiogram.

Summario in Interlingua

Septe patientes, subjicite a chirurgia a corde aperte pro le reparo de defectos ventriculoseptal, esseva studiate electro- e vectocardiographicamente ante e post le operation. Traumatic bloco de branca dextere esseva producite per le intervention chirurgic. In association con iste anormalitate del conduction, alterationes characteristic occurreva in le ansas vectocardiographic. Le characteristicas notate in le ansas pote esser utilisate in le differentiation inter bloco de branca dextere e hypertrophia dextero-ventricular in casos in que le electrocardiogramma es equivoc.

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In very many, and almost all kinds of Insects, by reason of the smallness of their Corpulency, we cannot rightly discern; yet in Bees, flies and wasps we may by the help of a perspective glass. You may likewise see something beat in lice, in which moreover you may clearly see the passage of the nourishment through the intestines (this Animal being transparent) like a black spot, by help of this multiplying glass. But in those that have no blood and are colder, as in Snails, Shell-fish, Crusted-Shrimps, and the like, there is a little part which beats (like a little bladder, or an ear) without a heart, making its contraction and pulse seldomer, and such a one as you cannot discern but in summer, or in a hot season.—William Harvey. *De Motu Cordis*, 1628.

Hemodynamic Studies in a Case of Carcinoid Cardiovascular Syndrome

By B. L. Charms, M.D., P. Kohn, M.D., H. I. Applebaum, M.D., and J. Geller, M.D.

NUMEROUS reports of cases of malignant carcinoid associated with acquired cardiovascular abnormalities have appeared in the medical literature since this syndrome was first recognized as a clinical entity. Despite the fact that the intracardiac abnormalities characteristic of this interesting disease are almost exclusively confined to the right side of the heart, catheterization studies have only infrequently been mentioned and no truly complete hemodynamic data have been included in the case reports published to date.

Of the valvular lesions encountered in the carcinoid cardiovascular syndrome, tricuspid insufficiency is the most frequently seen; right atrial tracings exemplifying this condition appear in the communications of Bjorck, Axen, and Thorson[1] and Sjoerdsma, Weissbach, and Udenfriend.[2] However, cardiac catheterization data supporting the diagnoses of tricuspid stenosis, pulmonary stenosis, and pulmonary insufficiency, which may also occur in association with functioning carcinoid, have not come to our attention.

Serotonin or 5 hydroxytryptamine (5-HT), the elaboration of which by the argentaffine cells has been generally accepted as the pathogenic agent responsible for the cardiovascular manifestations of malignant carcinoid, has been shown to produce pulmonary hypertension in animals.[3] The occurrence of pulmonary hypertension in the reported cases of carcinoid cardiovascular disease, however, has not been frequent. Sparks and Towbridge[4] reported that cardiac catheterization established the diagnosis of pulmonary hypertension in their case but the actual pressures were not stated. In McKusick's excellent review[5] mention was made of a patient with the carcinoid syndrome who was catheterized by Dr. Richard J. Bing in 1949, and who showed elevation of the pulmonary artery pressure. Unfortunately, neither clinical nor hemodynamic data relating to this patient were published.

Mattingly and Sjoerdsma[6] specifically stated that the 4 cases studied by them did not have pulmonary hypertension, although in one of the cases, cardiac catheterization was not done, and in another the catheter could not be passed from the right atrium into the right ventricle. In the remaining 2 cases, actual intracardiac pressures were not listed.[2]

Because of the relative paucity of reports dealing with detailed hemodynamic studies in the carcinoid cardiovascular syndrome, the following case is presented. It is also believed that this case is of general interest in that it so well typifies the extracardiac characteristics of this comparatively recently described disease.

Case Report

A 72-year-old Negro was first admitted to Mount Sinai Hospital of Cleveland on February 22, 1955, complaining of "liver trouble." Six months prior to hospitalization, he had first become aware of upper abdominal pain and it had become increasingly severe, particularly during the previous 3 or 4 weeks. This pain usually began following meals, but otherwise showed no particularly characteristic features. He had been a "moderate" drinker all his adult life. The outstanding finding on physical examination consisted of a markedly enlarged liver whose edge extended down to the umbilicus and was described as smooth and firm. The patient also had a marked purple-red discoloration of the face and, as a result, the diagnosis of polycythemia vera was actually con-

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sidered. Hematologic study, however, quickly ruled out this impression as it disclosed a moderate anemia. The red cell count was 3.60 million per mm.^{3}, hemoglobin was 10.4 Gm. per cent, and the hematocrit level was 37 per cent. Other blood chemical studies were normal.

The electrocardiogram showed frequent atrial and ventricular premature beats, left axis deviation, flat T in lead I, prominent P wave in leads II and aV_F, inverted T wave in aV_L and inverted T in V_{1-6}. The chest roentgenogram showed slight cardiac enlargement, the aorta was elongated and tortuous, and no pulmonary infiltration was present. An intravenous pyelogram showed a linear calcification in the midline and in the right lower quadrant, which was interpreted as a markedly redundant aorta with aneurysmal dilatation in the region of the aortic bifurcation and involving the right common iliac artery. There was minimal hydronephrosis of the right kidney, and hydroureter was present to the level of the aneurysm, beyond which the ureter was not seen. The barium enema was negative except for a diverticulum of the hepatic flexure. A gastrointestinal series was essentially negative.

The patient was discharged on March 5, 1955, with the diagnoses of Laennec's cirrhosis, aortic aneurysm, and arteriosclerotic cardiovascular disease.

The patient discontinued his use of alcoholic beverages and subsequently felt quite well until approximately July 1958, when he was again seen because of development of edema of the lower half of the body. He was treated with chlorothiazide and meralluride, to which he responded well. He developed mild intermittent diarrhea, which gradually increased in severity and occasionally contained blood. His appetite was not impaired, however, and there was no nausea or vomiting. Occasional upper abdominal distention was relieved by belching. In July 1958, his feet began to swell again and diuretics were started with some relief. The patient at no time complained of chest pain, exertional dyspnea, or paroxysmal nocturnal dyspnea. Periodic or paroxysmal flushing of the face had never occurred. Because of increasing diarrhea and a palpable hard abdominal mass in the right lower quadrant, the patient was readmitted.

Physical examination at this time disclosed telangiectases with purple-red discoloration on the face and forehead. Areas of stasis dermatitis were present over both lower legs. The heart was slightly enlarged to the left. A grade-II systolic murmur was heard best at the fourth and fifth intercostal spaces, just to the left of the sternum. The rhythm was regular. Examination of the abdomen disclosed the liver edge to be palpable 2 fingerbreadths below the costal margin. A mass of indefinite size and contour was present in the right lower quadrant. A large right inguinal hernia was noted. On rectal examination the prostate was felt to be enlarged, but smooth and with no masses. There was marked edema of the lower extremities extending up to the thighs.

Laboratory studies disclosed a hemoglobin of 9.8 Gm. per cent, hematocrit 29 per cent, white blood count 5,500 per mm.^{3}, differential normal, sedimentation rate 19 mm. per hour, prothrombin time 16.9 seconds, with control of 14.3 seconds, 3+ cephalin flocculation test, albuminuria, and 30 to 40 white blood cells per high-power field in the urine.

On the posteroanterior chest roentgenogram the heart appeared to be enlarged in the region of the left ventricle, but the high diaphragm seemed to contribute to this appearance. In the lateral view the left ventricle was definitely rounded posteriorly. There was no pulmonary infiltration.

The barium enema showed several scattered diverticula. A well-defined filling defect seen along the medial margin of the cecum was constantly visualized throughout the original filling with barium and on the subsequent air study. This filling defect was evidently produced by an amorphously calcified mass adjacent to the cecum and apparently continuous with the calcified aorta, which was previously demonstrated and described as a saccular aneurysm of either abdominal aorta or upper portion of the right iliac artery. A gastrointestinal series also showed a mass in the right lower quadrant separating some of the small bowel loops in this area but apparently not involving the small bowel intrinsically. Electrocardiogram showed only minor changes from the tracing of 1955, with lower amplitude of QRS and widened splintered S in leads II, III, aV_F, and V_6.

At laparotomy a large retroperitoneal tumor was found in the right lower quadrant behind the cecum and terminal ileum. Metastatic tumor was also noted in the liver and in the cul-de-sac. A biopsy of the liver and a peritoneal lymph node were taken, and an ileotransverse colostomy was done. During the operative procedure the anesthesiologist noted progressive increase in expiration time and resistance.

Histologic sections revealed the liver and lymph node to be partially replaced by a tumor composed of distinct nests of moderately sized cells. Their nuclear appearance was uniformly benign. The cytoplasm was relatively slight in amount and poorly defined. The cells tended to have an alveolated appearance and frequently exhibited central areas of cavitation and even adenoid for-

TABLE 1.—*Hemodynamic Data*

	Control	Occlude right main pulmonary artery	Occlude infuse 5 mg. resperine
Pressures mm.Hg			
Wedge	4-12		
Pulmonary artery	35/12 (18)	40/12 (23)*	35/10 (20)
Right ventricular	28/10		
Right atrium	8-22		
Brachial artery	115/65	105/65	105/65
Esophageal	+3 to –10	–1 to –9	+2 to –10
Percent saturation	92	93	
A-V difference (vol. %)	4.7	5.7	
Respiratory minute volume (L./min.)	6.5	5.3	
Oxygen consumption ml./min.	163	133	
Cardiac output L./min.)	3.4	2.3	

*Mean values.

mation. The adenoid cavities were filled with pink-staining material. An argentaffine reaction performed on the liver section showed the tumor to give a positive reaction. Stains for connective tissue revealed portal fibrosis, which tended to divide the liver tissue into nodular areas. No fatty change was noted. The diagnoses were secondary carcinoid tumor and portal cirrhosis. Subsequent tests for urinary 5-OH indole acetic acid were positive.

Cardiac catheterization was carried out in the usual manner. In addition, special studies including temporary unilateral pulmonary artery occlusion, as described elsewhere,[8] esophageal pressure determinations, and intravenous infusion of reserpine 0.5 mg. were obtained. The results of these hemodynamic studies are listed in table 1 and are shown in figures 1 and 2.

The data show (1) tricuspid insufficiency (fig. 1), (2) minimal pulmonary hypertension, (3) low cardiac output, (4) elevated end diastolic pressure in the right ventricle, (5) slightly increased intrathoracic pressure as evidenced by the elevated intraesophageal pressure, (6) probable absence of significant intrinsic pulmonary vascular disease as suggested by only a minimal (normal) rise in pulmonary artery pressure with temporary occlusion of the right main pulmonary artery,[8] and (7) slight fall in pulmonary artery pressure resulting from intravenous administration of reserpine (table 1 and fig. 2).

The patient was discharged from the hospital to be followed by his private physician.

DISCUSSION

Consideration of all the data in this case indicates that all the cardinal features of the carcinoid cardiovascular syndrome were present, including telangiectases with "cynotic" flush, diarrhea, bronchospasm, and a right-sided valvular heart lesion. Carcinoid tissue metastatic to the liver actively secreting 5 hydroxytryptamine was proved pathologically and by urinary excretion of 5 hydroxy indole acetic acid.

As noted above, the most common valvular lesion found in association with malignant carcinoid is tricuspid insufficiency and this disorder was most prominent in the present case. The explanation for the almost constant finding of tricuspid insufficiency is thought to be the endocardial fibrosis involving the right atrium and ventricle. This causes shortening and thickening of the chordae tendineae and prevents complete closure of the tricuspid valve. The exact mechanism by which the endocardium undergoes this fibroplastic change is poorly understood but is thought to result from the high concentrations of serotonin to which the right side of the heart is subjected. This occurs by virtue of its receiving almost directly the output of the argentaffine cells in the metastatic carcinoid tissue of the liver via the hepatic vein and inferior vena cava. That these lesions practically never occur on the left side of the heart is considered to be due to removal of the serotonin in the lungs by means of the enzyme mono-amine oxidase, which is found in the pulmonary vascular bed and which has been shown to inactivate the 5-OH tryptamine.[7]

In the case under consideration, the tricuspid insufficiency was thought to be responsible in great measure for the anasarca

and for the considerable reduction in cardiac output. The diastolic gradient existing between the right atrium and right ventricle was not considered to be great enough to justify the additional diagnosis of tricuspid stenosis. The cardiac catheterization data likewise failed to establish the presence of any lesion affecting the pulmonary valves.

As mentioned earlier, pulmonary hypertension has only rarely been found in the comparatively few cases in the literature in which cardiac catheterization has been performed. Unfortunately, in the 2 cases in which pulmonary hypertension was found, the actual level of the pulmonary artery pressure was not given. It is somewhat surprising that pulmonary hypertension has not been a prominent finding, in view of the very striking effect of infused serotonin on the pulmonary artery pressure of experimental animals. In our case, a minimal, although definite, elevation of the pulmonary artery pressure was found. Many explanations are actually available for the apparent paradox of a normal, or only minimally elevated, pulmonary artery pressure in the presence of a substance, 5 hydroxytryptamine, which has been shown to have such propensities for elevating the pulmonary artery pressure under experimental conditions. The most obvious explanation would be the circumstance that the cardiac catheterization was not performed during a "paroxysm" comparable to the periodic flush these patients often have during which presumably a large amount of 5-OH tryptamine is liberated into the circulation. Assuming, however, that this is not the factor, other theoretical considerations can be entertained. The nature of the right-sided cardiac lesions in the carcinoid syndrome, i.e., tricuspid insufficiency as in our case, or tricuspid stenosis and pulmonary stenosis, would of themselves tend to lower pulmonary artery pressure. The reduced cardiac output, whether primary or secondary to the anatomic lesion, would likewise operate in the same direction with respect to the pulmonary artery pressure. In contrast to acute experiments with serotonin, the patient with long-standing increase in circulating serotonin might be expected to have developed adaptive mechanisms, either reflex or enzymatic in nature, for more effective neutralization of the pulmonary hypertensive effect of the serotonin.

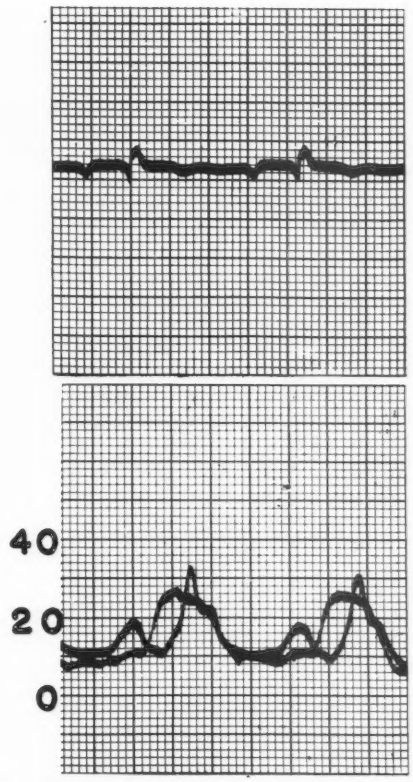

FIG. 1. Right atrial and right ventricular curves are superimposed showing the marked prominence of the atrial V wave and tricuspid insufficiency. The apparent overshoot of the V wave is thought to be an artifact. The pressures were obtained at the termination of the procedure after deflation of the cuff and are, therefore, lower than the figures given in table 1.

The esophageal pressure, as noted in table 1, was slightly elevated in our case, thus indicating a corresponding increase in the intrathoracic or intrapleural pressure. This was considered to reflect an element of bronchospasm with consequent elevation of the intra-alveolar pressure. That bronchospasm proved to be of clinical significance in

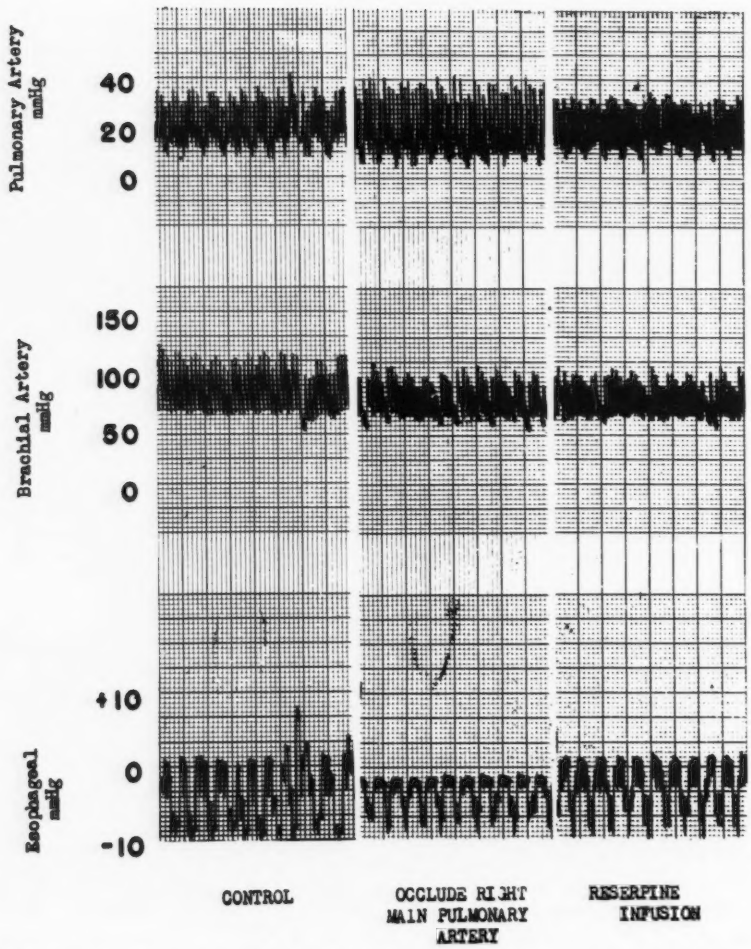

FIG. 2. Slow paper speed showing, from above down, pulmonary artery, brachial artery, and esophageal pressures. Control values are shown followed by those obtained after occlusion of the right main pulmonary artery. Reserpine was infused with the cuff still inflated so that these values must be compared with those immediately preceding.

this case was illustrated by the difficulty experienced by the patient during surgery when expiratory obstruction and air trapping developed. As is well recognized, increased bronchomotor tone is an important and frequent manifestation of the carcinoid syndrome and is likewise considered to result from the smooth muscle stimulating properties of serotonin. It is suggested that the slight elevation in pulmonary artery pressure in our patient was secondary to bronchospasm, either from circulating serotonin or mild emphysema.

Temporary unilateral pulmonary artery occlusion was included in our hemodynamic studies for the purpose of assessing the possible element of intrinsic pulmonary vascular disease in the carcinoid cardiovascular syndrome. The technic utilized and the results obtained in normal individuals with this

method have been described in detail elsewhere.[8] As noted in table 1 and figure 2, occlusion of the right main pulmonary artery with an inflatable balloon effected a rise in the main pulmonary artery pressure which was comparatively small and fell within the standards considered to be normal. This result provides evidence for the conclusion that no significant degree of involvement of the pulmonary vasculature existed in this case. Although numerous necropsy studies have been reported in cases of carcinoid cardiovascular syndrome, no description of the pulmonary vessels in this disease has come to our attention. In view of the profound fibroplastic effect of serotonin, presumably on the endocardium of the right atrium and ventricle, and the tricuspid and pulmonary valves, it appeared reasonable to speculate as to the probability of intimal proliferative changes in the pulmonary artery and its branches. However, in view of the normal response to unilateral pulmonary artery occlusion, it would seem highly doubtful that any degree of fixed pulmonary resistance, based on sclerotic changes in the pulmonary vasculature, existed.

Numerous pharmacologic agents have been described as antagonists to serotonin such as yohimbine, ergot, chlorpromazine, reserpine, atropine, and diphenylhydramine.[9-12] However, the only preparation that has ever been shown to have any clinical salutary effect on the symptoms of carcinoid is rauwolfia.[13] With reserpine infusion, a definite lowering of the pulmonary artery pressure ensued. This we considered to be significant inasmuch as no concomitant change in the brachial artery pressure occurred during the period of observation. It should be mentioned that approximately 1 hour after the administration of reserpine, the systemic pressure fell. The temporal response to reserpine was therefore quite different in the pulmonary and systemic circuits, suggesting a different mechanism of action in these circuits and supporting the concept that serotonin is inactivated in the lung.

Summary

A case of malignant carcinoid metastatic to the liver with the typical features of the carcinoid cardiovascular syndrome has been presented. Hemodynamic data obtained at cardiac catheterization indicated the presence of tricuspid insufficiency, low cardiac output, and slight pulmonary hypertension. Unilateral pulmonary artery occlusion studies were reported that suggest the absence of intrinsic pulmonary vascular disease in this syndrome. The paradox of infrequent instances of significant pulmonary hypertension in the presence of serotonin in the reported cases of carcinoid cardiovascular syndrome was discussed. The effect of reserpine on pulmonary artery pressure was reported.

Acknowledgment

We wish to thank Mrs. J. Germano and Misses S. Avsenek and M. Alford for their technical assistance.

Summario in Interlingua

Es presentate un caso de maligne metastase carcinoide al hepate, exhibiente le aspectos typic de carcinoide syndrome cardiovascular. Datos hemodynamic obtenite per catheterismo cardiac indicava le presentia de insufficientia tricuspidal, basse valores del rendimento cardiac, e leve grados de hypertension pulmonar. Studios a occlusion unilateral de arteria pulmonar suggereva le abentia de intrinsec morbo pulmono-vascular in iste syndrome. Es discutite le paradoxo del infrequentia de significative grados de hypertension pulmonar in le presentia de serotonina in le reportate casos de carcinoide syndrome cardiovascular.

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SCIENCE AND FEELING

J. Arthur Thomson

British: professor of natural history, editor and author; 1861-1933

Truly, science as science is unemotional and impersonal, and its analytic, atomizing, or anatomizing methods are apt, in their matter-of-factness, to seem antagonistic to artistic unities and poetical interpretations. But here must be learned the lesson of patience and openmindedness, and here the limitations of science must be borne in mind. The poetry of the men of feeling must not contradict th formulations of the man of science, but they are speaking different languages, and we may know by feeling some aspect of reality which eludes us in scientific analysis. Our delight in fine scenery is not less real than our knowledge of the geology. Both are pathways to reality. When science makes minor mysteries disappear, greater mysteries stand confessed. For one object of delight whose emotional value science has inevitably lessened—as Newton damaged the rainbow for Keats—science gives back double. Science widens and clears the emotional window. There are great vistas to which science alone can lead, and they make for elevation of mind.—*The Outline of Science,* Vol. 4, p. 1165. From *Great Companions, Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

A Cooperative Study of Cerebrovascular Disease

Methodology and a Preliminary Report on the Use of Anticoagulants

By ELLEN MCDEVITT, M.D., SIGMUND N. GROCH, M.D., AND IRVING S. WRIGHT, M.D.

Great interest continues in the treatment of cerebrovascular vascular accidents with anticoagulant agents. This paper presents a preliminary report of a cooperative study of this subject and indicates the methodology and protocol of the study, problems inherent in it, and preliminary findings of the first two years, without drawing definite conclusions.

ENCOURAGING reports on the favorable influence of anticoagulants in the treatment of cerebral embolism associated with heart disease and certain syndromes of cerebral artery disease have appeared in the world literature over the past 17 years.[1-7] Many of these studies have been either retrospective in nature or lacking in simultaneously studied, untreated control patients. Previous reports[8-10] from the Vascular Service at the New York Hospital-Cornell Medical Center have dealt largely with the long-term study of patients to determine the course of the disease process. The patients, for various reasons, had interruptions of their anticoagulant therapy, and thus served as their own controls. These studies were sufficiently encouraging to justify a long-term controlled study to evaluate the role of anticoagulants in both the acute and chronic phases of cerebral thrombosis. Therefore, the present study was developed to answer these and many other questions. Furthermore, it is based on a very carefully designed random sampling approach with parallel series of "control" and "treat" cases. In this way the value of anticoagulants in cerebrovascular disease is subjected to another type of test.

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Concurrent with, and at first independent of, the use of oral anticoagulants in the treatment of thromboembolism of the cerebral arteries, there appeared a revival of interest in and a clarification of these vascular syndromes. This interest was stimulated in part by the description of the clinical and pathologic findings associated with basilar artery thrombosis by Kubik and Adams.[11] Fisher[12] emphasized partial or complete occlusion of the cervical portion of the internal carotid artery as the site of lesions producing damage within the brain in which no demonstrable thrombosis of arteries within the cranial cavity were found. Intermittent insufficiency of both basilar and internal carotid arteries was then more fully described by Fisher,[13] and he reported encouraging results following the use of anticoagulants in the treatment of these syndromes. Comprehensive studies of the syndromes of intermittent insufficiency in the basilar and carotid artery systems have been published by Millikan and his co-workers.[14, 15]

The need being recognized for exchange of information among the different disciplines involved in the investigation and treatment of cerebral vascular disease, the first conference on Cerebral Vascular Diseases was organized under the chairmanship of Wright[6] and with the support of the National Heart Institute and the American Heart Association. As one of the results of this conference an ad hoc committee under the chairmanship of Millikan and supported by the National Institute of Neurological Diseases and Blindness was established for the consideration of co-

operative studies investigating these syndromes. The first work of this committee was that of clarification of the terminology involved in the description of the syndromes of cerebral arterial disease and their classification.[16]

At the same time efforts were being made to establish a cooperative study of these problems on the wards of the Second Medical and Neurological (Cornell) Divisions of Bellevue Hospital in New York City. After 3 years of preliminary planning and investigation, in July 1956 the study was inaugurated and this report is concerned with the results of anticoagulant therapy during the period July 20, 1956, to June 30, 1958.

The comprehensive goals of the study are as follows: (1) to obtain a clear delineation of the natural history of various syndromes associated with thrombotic or embolic diseases of the vascular system of the brain; (2) to re-evaluate accepted diagnostic procedures and to determine if possible their usefulness in the separation of the different syndromes; (3) to investigate within the limits of presently available technics the role of newer diagnostic aids: (4) to determine the presence or absence of concomitant coagulation defects; (5) to evaluate methods of determining psychiatric components of these diseases; (6) to evaluate the efficacy of anticoagulants in the treatment of various cerebral vascular syndromes and the prevention of recurrence of thromboembolism in extracranial sites; (7) to evaluate the role of a rehabilitation service in total recovery of function; (8) to coordinate pathologic findings with the clinical course in an attempt to clarify our understanding of these syndromes; (9) to subject data so obtained to rigorous statistical analysis; (10) and finally, to offer an opportunity for training and investigation in this field to interested physicians and ancillary personnel.

A study designed to investigate so many facets of a disease, requiring as it does the combined efforts of many individuals, cannot be initiated rapidly. It requires careful planning and close supervision. Hence 3 years were spent in the organization of the study plan or protocol. During this period, diagnostic criteria were re-examined, contraindications to anticoagulants were re-evaluated, medical and ancillary personnel were engaged and trained, laboratory facilities were established, and official and financial support was obtained.

Personnel

An advisory committee consisting of the medical coordinator and the chiefs of each of the services involved or their representatives determines official policy. In addition, the medical coordinator has had frequent consultations with the statistical advisor regarding the basis for the study plan.

The hospital physicians, laboratory assistants, physical therapists, social worker, study secretary, and the regular ward and clinic personnel are vitally concerned in the day-to-day operation of the study.

Methods and Materials

Administrative Details

Every patient admitted to the Medical or Neurological wards of the Second (Cornell) Division of Bellevue Hospital with a diagnosis of cerebrovascular disease is included in this study. Recently the patients from the medical wards of the First (Columbia) Division have been included. A careful history and physical examination, which is carried out by the ward physician, are obtained. Certain indicated diagnostic procedures necessary for the clarification of the definitive diagnosis, including an examination of the spinal fluid, are performed. Only then is the patient assigned to one of several categories: (1) should there be strong evidence that the diagnosis is that of cerebral embolism, the patient receives anticoagulant therapy and is thus removed from the anticoagulant study; (2) should there be evidence of cerebral hemorrhage or some other factor which would contraindicate the use of anticoagulants, the patient is also removed from this phase of the study; (3) when the diagnosis of cerebral thrombosis is made and when no known contraindications exist, the patient is submitted to the previously randomized selector system and an envelope is drawn from a box containing 100 envelopes, one half of which include a card stating "Treat" and the other half stating "Do not treat"; on the basis of the instructions within the envelope, the patient enters the

TABLE 1.—*Distribution by Age and Clinical Diagnosis, July 20, 1956 to June 30, 1958*

Ages	Emb.*	Hem.	Ins.	Throm. cerebral	Bas. artery	Int. car. artery	Throm. vs. emb.	Tumor	Indef.	Totals
To 19		2								2
20—30		1								1
31—40	2	6		2	1	1				12
41—50	3	6		6	3	1				19
51—60	3	9	2	35	12	4	1	4	4	74
61—70	10	8	5	54	9	10	1	1	3	101
71—80	5	7		46	5	2	3		2	70
81		1		15	2	2			2	22
Total	23	40	7	158	32	20	5	5	11	301
Age not known		2								
Total	23	42	7	158	32	20	5	5	11	303

*Emb., embolus; Hem., hemorrhage; Ins., insufficiency; Throm., thrombosis, distal and above the bifurcation of the internal carotid artery; Bas. artery, basilar artery system thrombosis; Int. car. artery, thrombosis of the carotid system at and proximal to the bifurcation of the internal carotid artery; Throm. vs. emb., occlusive vascular disease in which the diagnosis between thrombosis and embolism could not be definitely made.

control or treat group of the anticoagulant study.

While the patient is on the wards of the hospital, the daily anticoagulant therapy as well as the routine medical care is under the direct supervision of the ward physicians. Consultation with the Study Group is always available. Prothrombin times are performed daily and the dosage of the oral coumarin is adjusted according to the patient's needs. The prothrombin times are determined following the Link-Shapiro modification of the Quick test. The thromboplastin used gives control times of 14 to 16 seconds in the undiluted and 38 to 42 seconds in the diluted (12½ per cent) solution.

After discharge, patients receiving anticoagulants are seen in the Special Study Clinic at weekly intervals by members of the study group for regulation of anticoagulant therapy and evaluation of physical status. The patients not receiving anticoagulants are maintained on placebo therapy and are seen at less frequent intervals.

The oral coumarins used in this study are those provided by the pharmacy of Bellevue Hospital (Dicumarol and Warfarin sodium). Vitamin K_1 has been employed to reduce prothrombin times to within therapeutic range or to a normal value in instances where they are excessively high or where significant bleeding has occurred. Whole blood has been used only for the replacement of excessive blood loss.

Description of Total Series

The hospital at which this study is being conducted is a large municipal hospital concerned with general medical care and is part of the Department of Hospitals of the city of New York. It serves a population of various racial, cultural, and economic backgrounds. A large portion of the hospital population is composed of transient patients who may be difficult to follow medically for prolonged periods of time. An active ambulance service insures the inclusion of many severely ill patients. There is no selective medical admission policy enforced because the need for medical care is usually the indication for admission.

New patients are admitted in rotation to 4 separate medical services and there is no apparent bias in distribution of categories of patients. The medical services are an integral part of the university teaching programs of 3 medical schools in the city of New York, namely, those of Cornell, Columbia, and New York Universities.

Three hundred and three patients with the diagnosis of cerebrovascular disease were admitted to the cooperating wards during this phase of the study. There were 183 males and 120 females. This probably represents the distribution of male and female patients for the medical and neurological ward population.

The distribution according to diagnosis and age is shown in table 1. The peak incidence of admission in all categories occurred in the decade 61 to 70, and the most frequent clinical diagnosis was that of cerebral thrombosis of the internal carotid system above the bifurcation into the middle cerebral and anterior cerebral arteries. The 3 individuals below the age of 30 were patients with subarachnoid hemorrhage secondary to congenital aneurysm. The composition of the entire series is

TABLE 2.—*Composition of Series*

Total number	Sex M	Sex F	Control*	Treat*	Obligatory treat	Never drawn
303	183	120	51	53	39	160

*By selector system.

TABLE 3.—*Obligatory Treats*

Diagnosis		Died On	Died Off	Alive On	Alive Off	Lost to follow-up
Rheumatic heart disease	16	3	2	4	6	1
Arteriosclerotic heart disease—myocardial infarction	6		3	1	2	
Basilar	9	4		2	3	
Internal carotid	3			2		1
Thrombophlebitis	5	2	1	1	1	
Totals	39	9	6	10	12	2

shown in table 2. Sixty-one patients were immediately excluded from the study group on the basis of the initial physical or laboratory examination. The spinal fluid of 29 patients was grossly bloody, and in 15 xanthochromic supernatant spinal fluid was observed. Medical contraindications excluded 17; 9 of these were markedly hypertensive, 3 had evidence of recent gastrointestinal bleeding, and 5 others were excluded because of presence of liver disease, active duodenal ulcer, blood dyscrasia, or other reasons.

Ninety-nine patients were not considered to be suitable for the following reasons: 64 were either so critically ill that adequate evaluation for the study was not feasible or they died before evaluation was possible. In 7 instances, spinal fluid examination was refused or the puncture was traumatic. Fourteen were immediately transferred to other institutions or were unsuitable for follow-up study. In 7 the diagnosis could not be clearly established and thus these patients were unsuitable for a controlled study. In 7 patients the focal signs and symptoms suggestive of cerebrovascular disease were produced by other lesions; in 5 of these the presence of an expanding lesion was demonstrated and in 2 instances a subdural hematoma was found. These patients will form the basis of a subsequent report.

On the basis of the instructions enclosed in the previously randomized envelopes, 51 patients were admitted to the group not receiving anticoagulants and 53 admitted to the group receiving anticoagulants. The remaining 39 patients received anticoagulants because they were considered to present complications or concomitant evidence of thromboembolism, which made their treatment with these substances mandatory. In this group are included those individuals who presented signs and symptoms of cerebral embolism secondary to rheumatic heart disease or myocardial infarction, or who developed thrombophlebitis and in whom the possibility of fatal pulmonary infarction presented a real threat to life. In addition, in the early months of this study patients were included in this group with either basilar artery thrombosis or insufficiency or carotid artery thrombosis or insufficiency. These 3 groups will therefore subsequently be referred to as "the control," "the treat," and "the obligatory treat" groups. While patients were in most instances admitted to the study within 7 days of their stroke, they were considered eligible for admission up to 2 months. Anticoagulants were not usually begun until at least 36 hours had elapsed, except where diagnosis of basilar artery disease was made.

RESULTS

Obligatory Treats

The distribution and present status of patients within this group are shown in table 3. Sixteen of the 39 patients in this group had rheumatic heart disease. Of these 16, there have been 5 deaths, 3 occurring while the patients were still receiving anticoagulants and 2 after treatment was discontinued. In 1 individual a bloody spinal fluid was interpreted as a traumatic tap, and treatment was instituted before the study group saw the patient. A subsequent angiogram demonstrated a congenital aneurysm. This patient is among the 6 in whom no further thromboembolic complications have been observed after anticoagulants were discontinued. Four patients remain on anticoagulants and 1 has been lost to follow-up study.

Six patients had concurrent myocardial infarction or were thought to present significant premonitory signs of impending infarction. Three of this group are dead; 1 did not receive anticoagulants and 2 died after treatment was discontinued, 1 of myocardial infarction and 1 following coma, the cause of which was undetermined.

Nine patients with evidence of basilar artery disease were included in this group during the earlier phases of the study. Four of these have died, 2 of whom were in coma at the time of admission to the study. Anticoagulants have been discontinued in 3, and 2 remain

on anticoagulants. In 1 of these anticoagulant therapy was discontinued temporarily following traumatic fracture of the tibia.

Three individuals with thrombosis of the internal carotid or common carotid (1 bilateral) arteries were also included in this group early in the study. Two remain on anticoagulants and 1 has been lost to follow-up study. The patient with involvement in both carotid arteries voluntarily discontinued therapy for 2 weeks but has now resumed treatment.

Five patients developed associated thrombophlebitis. There have been 3 deaths in this group of 5. One patient, who initially showed a xanthochromic spinal fluid, was given heparin because of a rapidly ascending thrombophlebitis. She died, and at necropsy there was evidence of old infarction and recent hemorrhage in the brain stem. One patient developed hematuria, anticoagulants were discontinued, hematuria ceased, and the patient died 7 days later of the initial cerebral thrombosis. One patient remains on anticoagulants. The other patient is alive and not receiving anticoagulants.

Study Sample

Status of follow-up in the study group is shown in table 4. Twenty-three in the treated group and 29 of the control group remain in the originally designated categories as determined by the selector system. Seventeen patients in the treated group are alive but no longer receiving anticoagulants. Nine patients in the treated group have died; 1 of these never received anticoagulants. Fourteen patients in the control group have died, including 1 patient who received anticoagulants for a thromboembolic complication. Four additional patients in the treated group who did not receive anticoagulants are alive and have no further complications. In the control group 3 patients received anticoagulants following a single thromboembolic complication and are still alive.

Thromboembolic Complications

The percentage of complications in the control and treated groups are contrasted in figure 1. There were 10 thromboembolic (20 per cent) complications in the control group, including 3 pulmonary emboli, 1 peripheral embolus, 2 myocardial infarctions, 2 thrombophlebitis. There was 1 recurrence of a cerebrovascular thrombosis and 1 extension of the initial lesion. Four of these patients received anticoagulants after the complication occurred. In 6 the complications were considered to be the major cause of death.

TABLE 4.—*Status of Follow-Up as of June 30, 1958*

	Still following original selector card	Discontinued anticoagulants; living; no thromboembolic complications	Died	Original selector card not followed	Lost to follow-up
Treated group	23	17	9*	4‡	0
Control group	29	—	14†	3§	5

*One patient did not receive anticoagulants.

†One patient developed a thromboembolic complication, received anticoagulants temporarily.

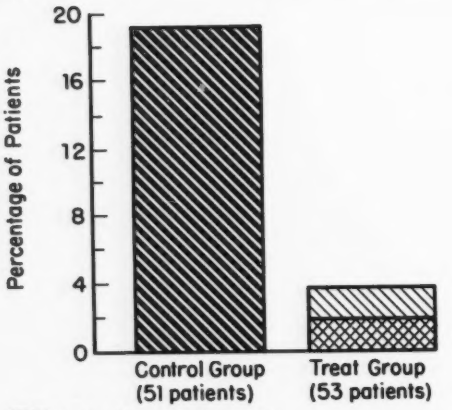
‡Did not receive anticoagulants though drawn "treat."

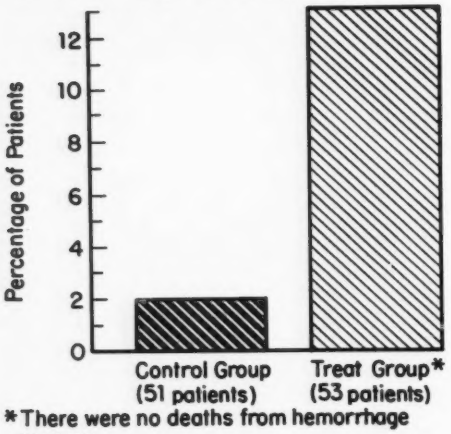
§Developed thromboembolic complication and received anticoagulants after drawn "control."

In the treated group of 53, there were 2 so designated who experienced thromboembolic complications. One complication occurred after anticoagulant therapy had been discontinued for 65 days and in the other an extension of the initial thrombosis was noted during a period when anticoagulant therapy was not at optimum level. The nearest prothrombin time was 20 seconds.

Hemorrhagic Complications

Figure 2 compares the percentage of hemorrhagic complications in the treated and the control groups (13 and 2 per cent respectively). There were no deaths due to hemorrhage in the treated group. There was 1 instance of massive cerebral bleeding resulting in death in the control group. This indvidual had not received anticoagulants. In the treated group the bleeding episodes were as follows: 1 patient bled around a tracheotomy site; 2 developed hematuria associated with prostatic disease; 1 patient had an intracerebral hematoma that may have existed before the administration of the anticoagulants; 1 patient





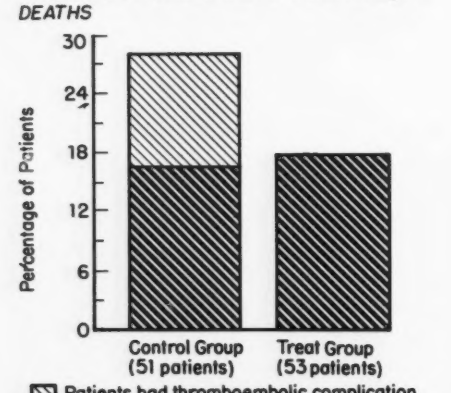


FIG. 1 *Top.* Incidence of thromboembolic complications in untreated and treated patients.

FIG. 2 *Middle.* Incidence of hemorrhagic complications in untreated and treated patients.

FIG. 3 *Bottom.* Mortality rate in untreated and treated patients.

had minor subcutaneous bleeding; 1 patient was found to have a silent carcinoma of the bowel; and the remaining patient developed a hematoma in the wall of the jejunum resulting in intestinal obstruction.

Deaths

The total deaths in the control group from all causes numbered 14 (28 per cent). In the treated group there were 9 (17 per cent). Six of the 14 patients dying in the control group had a clinically diagnosed thromboembolic complication after the initial cerebral lesion. As indicated in figure 3, there were no deaths in the treated group as a result of a subsequent thromboembolic episode. In the control group 6 of 51 patients (12 per cent) died with thromboembolic complications. Forty-three per cent of the deaths (6 out of 14) were due to such complications. Other causes of death in the control group were as follows: cerebral hemorrhage, 1; pneumonia, 1; pulmonary tuberculosis, 1; congestive failure, 1; trauma, 1; barbiturate toxicity, 1; and in 2 the cause of death was undetermined. In the treated group there were 9 deaths or 17 per cent of 53 patients. The causes of death were as follows: initial cerebral lesion, 3; congestive heart failure, 2; uncontrolled diabetes, 1; pneumonia, 1; pyelonephritis, 1; and 1 patient who was transferred to another institution died in coma, cause undetermined.

In the group of 160 patients for whom the selector system was not utilized and who did not receive anticoagulants, there have been 86 known deaths or 51 per cent. Three of these patients have been lost to follow-up and 71 were alive at last follow-up examination.

Mortality for the Series is Presented in Table 5

Twenty-six of the 61 patients who were found to have contraindications to the use of anticoagulants have died. This represents 44 per cent of the patients in this category. In the "Never Drawn" group of 99, the mortality has been 60 patients, or 60 per cent. Among the 39 patients considered to require obligatory anticoagulant therapy, 15 have died, a percentage of 38. The over-all necropsy

rate for the entire group is 35 per cent. Complete pathologic material will be presented at a later date.

Discussion

In the planning of this cooperative study previous experience in the cooperative study on myocardial infarction conducted by the Committee on Anticoagulants of the American Heart Association was of great assistance.[17] Certain difficulties encountered in that study were anticipated if not completely eliminated in the present one. Cooperative efforts, whether inter- or intra-institutional in scope, require careful planning far in advance of the actual initiation of the study. Careful supervision by a competent statistical consultant is essential, particularly during the planning and analysis stages. Records should be kept up to date and separate from regular hospital records and in a form in which they will be readily available for analysis.

Once the protocol has been formulated and criteria for admission to the study established, the conditions of the study must be rigidly maintained. It may become difficult or even impossible to achieve this goal because of the desires of physicians other than those in the study group either to include or to exclude individual patients from the study.

The present study exemplifies certain limitations that are inherent in projects of this nature. Language barrier and aphasia may make it impossible to obtain an adequate history. Certain bias is present in this sample as the hospital population is composed of individuals representing income levels lower than are generally prevalent. The incidence of multiple system disease is greatest in the older age group which is represented here. The nutritional state of many of the patients in this group is not at optimum level, either through habit or economic necessity, and may result in increased sensitivity to anticoagulants. More seriously ill patients are more likely to be admitted to institutions that have an active ambulance service, as this hospital has. Patients with lesions not on the dominant side are less likely either to seek hospital admission or to be admitted by their families.

Table 5.—*Deaths for Entire Series July 20, 1956 to June 30, 1957*

	Contra-indicated	Never drawn	Obligatory treat	Control	Treat
Total number	61	99	39	51	53
Deaths	26	60	15	14	9
Percentage	43.0	60	38.4	27.4	17.0

Further, since this is a progressive study and patients are continually being admitted, periods of observation vary from patient to patient. However, in the group designated control or treat by the previously randomized selector system employed in this study, such influence should be equally distributed among the control and treat patients and thus not bias the results in either group.

Since all aspects of medical care are not under the control of the study group, certain arbitrary decisions have been made by other members of the staff regarding the use or withdrawal of anticoagulant therapy. While this is rare, it is at present beyond the jurisdiction of the study group, but may prejudice to some degree certain results, particularly in the obligatory group.

Certain ancillary laboratory tests have been helpful in clarifying the underlying cerebral lesion. Spinal fluid examination remains one of the most important and anticoagulants should not be given without such an examination. Xanthochromic fluid is an absolute contraindication to immediate anticoagulant therapy and should not be ignored even if other significant thromboembolic complications develop. The electrocardiogram is an essential part of the examination of any patient with evidence of cerebral vascular disease, for myocardial infarction is frequently associated with the appearance of cerebral signs of focal nature. As demonstrated by Schwab,[18] serial electroencephalograms may be helpful in differentiating cerebrovascular disease due to cerebral thrombosis from tumor or intracerebral hematoma. Visualization of cerebral vascular structures by angiography is of particular assistance in establishing the diagnosis when an adequate history is not available for any reason. The results of angiographic stud-

ies in a series of patients with an initial clinical diagnosis of cerebrovascular disease is to be published elsewhere.

In selected cases, the use of the ophthalmodynamometer has been valuable in the diagnosis of thrombosis of the internal carotid artery. This experience will be reported elsewhere.

It is too early in this study to make definitive statements regarding this series of patients either as a whole or specifically as to the role of anticoagulants in the treatment of cerebral thrombosis. However, certain features merit discussion.

Among the 160 patients in whom contraindications to anticoagulant therapy were present or who were never drawn in the selector system, there were 2 instances of subdural hematoma and 5 of brain tumors, once again emphasizing the need for careful evaluation of each patient presenting signs and symptoms seemingly of vascular disease of the brain.

Ten (20 per cent) of recognizable thromboembolic episodes occurred in the control group after the initial cerebral lesion. In contrast, there were 2 further complications in the treated group, an incidence of 4 per cent. No thromboembolic complications occurred when patients were within therapeutic range. One extension occurred when the prothrombin time was not at optimum level; and the other patient who had been taken off anticoagulants because of melena associated with unsuspected carcinoma of the large bowel had a minor cerebral thrombotic episode on the other side 2 months and 5 days after therapy had been stopped. Anticoagulants were then restarted and the patient has been free of further thromboembolic complications. Thus 20 per cent of patients in the control group, but only 4 per cent of the treated group, developed a thromboembolic complication—a difference of 16 per cent between the 2 groups. At this time statistical significance, while borderline, is not conclusive.

There was a substantial difference, 11 per cent, between the percentage of patients with hemorrhagic complications in the treated and in the control group. This increase in instances of hemorrhage reflects the hazards associated with anticoagulant therapy in elderly patients with multiple system disease under the conditions of the present study. In 5 patients with bleeding while on anticoagulant therapy there were complicating extracerebral lesions. This confirms our previous experience with patients under therapy for thromboembolic complications. Bleeding frequently occurs in association with unsuspected pathology.

When the percentage of deaths in each category is considered, the figures in the obligatory, contraindicated, and never drawn groups reflect the serious nature of these syndromes and the frequency with which they are associated with unrelated diseases. Twenty-eight per cent of the control group have died during the period of observation, as compared with 17 per cent of the treated group. The difference of 11 per cent in the death rates of the 2 groups appears to reflect the benefit of anticoagulant therapy in view of 2 considerations: 1. The comparability of the rates when deaths in patients having no thromboembolic complications are considered. These rates were 17 per cent of the control and 17 per cent of the treated group. 2. The fact that no deaths in the treated group and 43 per cent of the control deaths were preceded by recurrent thromboembolic complications. Four of the control group, having received anticoagulants after developing an additional thromboembolic complication, died after anticoagulant treatment had been discontinued.

The prognosis for any given patient is difficult to establish. The vagaries of these syndromes are marked. In general, coma is an ominous sign, but many patients have recovered and had no residual.

In this series the indications for tracheotomy have been carefully considered and this procedure, if necessary, is now done early in the course of illness, preferably before anticoagulants are administered.

While all the facets of this problem as described in the initial protocol have not been

fully explored, the results to date are encouraging and the study merits continuation.

Summary

A design for cooperative study of diseases of cerebral arteries has been described. A preliminary report on the course of 303 patients admitted to the study has been presented. Patients receiving anticoagulants in the designated treat group have the lowest mortality and lowest rate of thromboembolic complications. They have an increased incidence of hemorrhage, but there have been no deaths in this group from hemorrhage.

Acknowledgment

The authors wish to acknowledge the assistance of Dr. Irwin Bross, Professor of Biometries in Public Health and Preventive Medicine, during the initial stages of planning this study.

Summario in Interlingua

Es describite un programma de studios cooperative de morbos del arteries cerebral. Un reporto preliminar del curso de 303 patientes includite in le studio es presentate. Le gruppo de patientes tractate con anticoagulants habeva le plus basse mortalitate e le plus basse frequentia de complicationes thromboembolic. Lor incidentia de hemorrhagias esseva augmentate, sed nulle morte per hemorrhagia ha occurrite in le gruppo.

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Effect of Smoking on the Fasting Blood Sugar and Pressor Amines

By KAI REHDER, M.D., AND GRACE M. ROTH, PH.D.

When 24 normal subjects under basal conditions smoked two thirds of 2 cigarettes, there was no appreciable rise in the levels of the fasting blood sugar and the epinephrine-like substances of the systemic venous blood. However, the smoking of two thirds of 2 cigarettes significantly raised the blood pressure and pulse rate, and decreased the skin temperature of fingers and toes.

EVIDENCE has been presented by various investigators that smoking of cigarettes causes transient hyperglycemia in human beings. Haggard and Greenberg,[1] Caponnette,[2] Töppner,[3] Burstein and Goldenberg,[4] and Lundberg and Thyselius-Lundberg[5] found in nondiabetic habitual smokers an increase in the level of the fasting blood sugar after smoking and a similar effect was produced by intramuscular injection of nicotine in some animals studied but not in all.[2] The parenteral injection of various amounts of nicotine into animals caused a mild to moderate transient hyperglycemia according to Nicolaysen,[6] Leloir,[7] Wilson and DeEds,[8] Mosinger and associates,[9] Kobayashi,[10] and Hazard and Vaille.[11]

On the other hand, there is also evidence that a change in the concentration of blood sugar does not take place after smoking. Dill, Edwards, and Forbes[12] reported that 90 per cent of their 60 subjects did not have a significant increase in the level of the fasting blood sugar after smoking. Furthermore, Cristol[13] could demonstrate no change in the level of the fasting blood sugar in 175 medical students after each had smoked three fourths of 2 cigarettes. Ssalischtscheff[14] was the only investigator who observed hypoglycemia during smoking by 5 nonsmokers and 6 smokers, but all his subjects showed signs of nicotine intoxication when the determinations of the blood sugar were done.

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The question arose as to whether the blood sugar in normal persons who smoked habitually could be significantly elevated by smoking. Because this elevation has been suggested by Kobayashi,[10] Leloir,[7] and Haggard and Greenberg[1] to result from the discharge from the adrenal gland of epinephrine or norepinephrine on smoking, the present investigation was begun.

METHODS

Blood sugar, pressor amines in the plasma, skin temperatures of the fingers and toes, blood pressures and pulse rates were determined before and after smoking on 24 male subjects (all physicians) whose ages ranged from 26 to 35 years.

Preliminary Studies. The subjects fasted for 15 hours before the tests, and during the tests they wore lightweight shorts and T shirts and were in a supine position on a comfortable bed in a constant temperature room at 25.5 C. with a relative humidity of 40 per cent. All unnecessary noises and other stimuli likely to cause vasoconstriction were excluded during the test.

The skin temperatures of the plantar surfaces of the first and third toes of both feet and the volar sides of the distal phalanges of the first and third fingers of both hands were measured by means of copper constantin thermocouples designed by Sheard[15] at 10-minute intervals for an hour. During this time the basal metabolic rate was determined, and the blood pressures and pulse rates were measured at 10-minute intervals.

When the skin temperature, blood pressure, and pulse rate were fairly well stabilized, a siliconized needle was inserted into an antecubital vein, and without the use of a tourniquet 3 samples of blood of 1 ml. each were collected at intervals of 1 minute. An additional sample of 15 ml. of blood was withdrawn for the determination of the pressor amines.

Blood Sugar and Epinephrine-like Substances. The determinations of fasting blood sugar were carried out in duplicate by the Somogyi-Nelson method.[16, 17] This method was used because it measures only glucose in contrast to the Folin-Wu and Hagedorn-Jensen methods, which measure all reducing substances in the blood. The blood for determination of sugar was rendered incoagulable by adding 2 drops of heparin to each 1 ml. and by keeping it in a refrigerator during the test. The pressor amines in plasma were estimated as total epinephrine-like substances by the method of Weil-Malherbe and Bone.[18]

Smoking. The subjects then smoked in succession two thirds of each of 2 filtered cigarettes. All but one inhaled the smoke with the depth and frequency to which they were accustomed. The blood pressure, pulse rate, and skin temperature were determined simultaneously at intervals of 1 minute during the smoking, which lasted 6 to 17 minutes, and for 13 to 24 minutes after smoking had ceased. At intervals of 3, 5, 10 and 15 minutes after smoking was begun, 1 ml. of blood was drawn for determinations of blood sugar and 15 ml. of blood was obtained between the third and fifth minutes for determination of the pressor amines. A final sample for determination of pressor amines was taken 15 minutes after smoking had ceased.

Cold Pressor Test. A cold pressor test was performed on each individual after the study was finished.

Control Group. Another 3 subjects were tested under essentially the same circumstances without smoking. They served as a control group.

Results

Blood Sugar. A total of 382 determinations of fasting blood sugar were performed on 24 healthy male individuals, 146 prior to smoking, 158 during smoking, and 78 after smoking. An additional 40 determinations were carried out on 3 subjects who did not smoke and served as a control group. No change in the mean level of the fasting blood sugar was observed before, during and after smoking (table 1). The mean values for blood sugar before smoking ranged from 69.0 ± 1.0 to 67.0 ± 1.0 mg. per 100 ml., and during and after smoking from 68.0 ± 1.0 to 69.0 ± 1.0 mg. per 100 ml. The maximal observed increase of the blood sugar during smoking was 9 mg. per 100 ml. and the maximal decrease was 10 mg.

TABLE 1.—*Mean Blood Sugar Response of Twenty-four Normal Individuals to Smoking of Cigarettes*

Time (min.)	Blood sugar (mg. per 100 ml.) Mean*	S.D.†	Epinephrine-like substances (μg. per 100 ml.) Mean*	S.D.†
Before smoking				
4			2.4±0.2	1
3	69.0±1.0	8.0		
2	67.0±1.0	6.0		
1	67.0±1.0	7.0		
During smoking for:				
3	68.0±1.0	9.0	2.4±0.2	1
5	68.0±1.0	8.0		
10	68.0±1.0	7.0		
15	68.0±1.0	8.0		
After smoking				
30	69.0±1.0	9.0		

*The number following the ± is the standard error of the mean.

†S.D., standard deviation.

In one study the second cigarette was not offered until the skin temperature had almost reached its normal value. This corresponded to an interval of 30 minutes between the 2 cigarettes. Again, we were unable to find any significant hyperglycemia. In 2 further studies, determinations of blood sugar were carried out 46 minutes after the patient finished smoking. Again no definite increase of the level of the blood glucose could be detected. The mean level for blood sugar of the control group who did not smoke ranged from 71.0 ± 2.0 to 74.0 ± 2.0 mg. per 100 ml. before the test and from 67.0 ± 3.0 to 71.0 ± 2.0 mg. per 100 ml. during the same period that the other subjects smoked. Thus no significant change occurred in the levels of blood sugar during and after the smoking in the group that smoked nor at any time in the control group.

Epinephrine-like Substances (Pressor Amines). Forty-eight determinations of epinephrine-like substances were carried out. Twenty-four were made 4 to 5 minutes prior to smoking, 22 between the third and fifth minutes of smoking and two 1 minute after smoking. Before smoking, the concentrations of epinephrine-like substances ranged from 0.7 to 4.0 μg. per 100 ml. of blood with an average of 2.4 ± 0.2 μg. (table 1). The mean value

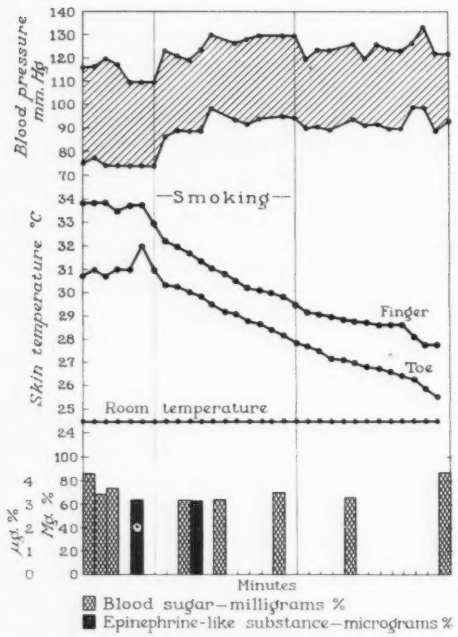

FIG. 1. The effect of smoking two thirds of two standard cigarettes on the cutaneous temperature of the extremities and blood pressure on the same subject. Note the fall in skin temperatures and the rise in blood pressure during smoking and after cessation. Also note the insignificant change in blood sugar and plasma pressor amines before and during the same period of smoking.

for pressor amines 3 to 5 minutes after beginning smoking showed no differences as compared with the mean values before smoking. Thus no change occurred.

Skin Temperatures. Before smoking the temperature of the fingers ranged between 24.6 and 35.3 C., with a mean value of 32.0 ± 0.3 C. After smoking the skin temperature of the fingers decreased to 22.9 to 33.1 C., with an average of 28.0 ± 0.3 C.; 9.8 C. was the maximal and 0.2 the minimal decrease observed in the skin temperature of the fingers after smoking. The temperature of the toes ranged from 22.3 to 34.3 C., with an average temperature of 27.3 ± 0.3 C. After smoking the skin temperature of the toes ranged from 21.9 to 29.7 C., with a mean temperature of 25.4 ± 0.2 C. The maximal observed decrease of the temperature of the toes was 5.7 and the minimal change 0 C. The greatest decrease of the temperature of the fingers as well as of the toes occurred most commonly between 20 and 30 minutes after the smoking was begun. The mean temperature of the fingers decreased 4 C. while that of the toes decreased 1.9 C.

The average change in the skin temperature of the nonsmoking group was as follows: fingers 0.7 and toes 1.1 C.

Blood Pressure. The average basal blood pressure of the 24 subjects was 103 ± 1 mm. Hg systolic and 72 ± 2 mm. diastolic. The systolic pressures ranged from 90 to 120, while the diastolic pressures ranged from 58 to 90 mm. The mean systolic pressure during smoking was 124 ± 2 mm. and the mean diastolic pressure was 88 ± 1 mm. The observed increment in systolic pressure ranged from 10 to 36 mm., and in diastolic pressure from 4 to 30 mm. The maximal systolic pressure occurred after 7.6 minutes of smoking, and the maximal diastolic pressure was observed after 4.5 minutes (fig. 1).

The 3 control studies revealed a mean pressure of 111 ± 2 mm. systolic and 78 ± 2 mm. diastolic, which increased during the time corresponding to smoking of the other subjects to 118 ± 4 systolic and 85 ± 3 mm. diastolic. The greatest change in blood pressure was associated with venipuncture for withdrawal of blood.

Pulse Rate. The mean pulse rate of the 24 individuals was 63 ± 2 beats per minute before smoking. During smoking the mean pulse rate increased to 86 ± 2, while in the 3 control subjects the mean pulse rate of 70 ± 4 before blood was withdrawn rose to 73 ± 5 during and after blood was drawn.

Cold Pressor Test. The mean systolic pressure increased from 108 to 140 mm. while the diastolic pressure rose from 76 to 104 mm. during the cold pressor test. Twenty two of the volunteers were grouped as vascular hyperreactors; only 2 were called "normal reactors."

Discussion

The question may arise as to whether our subjects did absorb the nicotine or whether they smoked cigarettes with low nicotine content. However, the significant rise of the pulse rate and blood pressure and the decrease of the skin temperature of the fingers and toes showed definitely a stimulation of the sympathetic nervous system. Indeed, the effect on the blood pressure, pulse rate, and skin temperatures shows a remarkable agreement with those reported previously by one of us.[19, 20]

The controversy in regard to the elevation of the fasting blood sugar by smoking has continued over a period of years. In an attempt to resolve this question, this investigation was carried out under basal conditions, in a constant temperature room and in a supine position. All possible psychic and physical stimuli were excluded. The venipuncture was carried out before the smoking began and the siliconized needle remained in the vein without another venipuncture, thus avoiding further somatic stimuli. Under these conditions, in contrast to the observations of most other investigators, no increase of the fasting blood sugar was observed during and after smoking. Likewise the smoking of 2 cigarettes with a longer interval of 30 minutes between the smoking of the first and second cigarette did not influence the blood sugar. The epinephrine-like substances in the venous blood also remained unchanged during as well as after smoking. Apparently the amount of secreted epinephrine-like substances in the systemic circulation was not sufficient to raise the total epinephrine-like substances in the blood, as measured with the Weil-Malherbe and Bone method, nor to increase the fasting blood sugar.

Summary

When 24 normal subjects under basal conditions smoked two thirds of 2 cigarettes, there was no appreciable rise in the levels of the fasting blood sugar and the epinephrine-like substances of the systemic venous blood. However, the smoking of two thirds of 2 cigarettes significantly raised the blood pressure and pulse rate, and decreased the skin temperature of fingers and toes. The conclusion may be drawn, therefore, that the smoking of cigarettes is not a likely cause of erroneous diagnosis of diabetes mellitus owing to the elevation of the blood sugar.

Summario in Interlingua

Quando 24 subjectos, sub conditiones basal, fumava duo tertios de 2 cigarettas, nulle appreciabile augmento esseva notate in le nivellos del suero de sanguine in stato jejun e del substantias epinephrinoide del sanguine venose systemic. Tamen, le fumar de duo tertios de 2 cigarrettas augemtava significativemente le tension del sanguine e le frequentia del pulso e reduceva le temperatura cutanee in le digitos manual e pedal. Nos pote concluder, per consequente, que le fumar de cigarettas non es un causa probabile de un diagnose erronee de diabete mellite super le base de un elevation non-diabetic del suero del sanguine.

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Various stages in the evolution of the renal lesions of malignant nephrosclerosis were present at necropsy in 100 patients with the clinical diagnosis of severe essential or malignant hypertension. Of the 100 patients, 19 were found to have evidence of "healing" or regression of the acute destructive lesions of malignant nephrosclerosis; all of these 19 patients had been under treatment with patent antihypertensive agents. The most dramatic regression of the lesions occurred in patients under therapy for at least 4 months. The untreated patients possessed vascular changes in the small arteries and arterioles, whereas the treated patients had extensive subintimal fibrosis in the large arteries which, in some instances, had progressed to vascular occlusion. It is the latter lesion which presumably led to the slowly progressing renal failure which was the cause of death in a majority of the treated patients in the group. The hypertensive state is presumed to result in damage to large and medium-sized arteries which may, in part, contribute to the subsequent appearance of atherosclerosis and intimal hyperplasia even though the arterial pressure may be more or less controlled. Lastly, it appears that the acute destructive vascular lesions of malignant nephrosclerosis are caused by increased arterial pressure.

Karpman

Formation of the "P-R Segment"

By Cesar A. Caceres, M.D., George A. Kelser, Jr., M.D., and W. Raymond Mize, M.D.

Variance of opinion among authors regarding the cause and duration of each succeeding portion of the P-R interval points out that knowledge regarding the physiologic basis for these waves is incomplete. Data regarding the P-R segment are scant in electrocardiographic literature. The necessity for precision in measurement and the need for better visualization of electrocardiographic waves to enhance their diagnostic value are illustrated by study of the generally ignored region between the P and QRS.

THE purpose of this report is to present data and tracings that define the region of the P-R segment more precisely than usual in clinical practice. By more precise measurement and better visualization of that portion of the electrocardiographic wave, factors of significance to its formation and of importance to the interpretation of the entire electrocardiogram are demonstrated.

Materials and Methods

The electrocardiograms studied were from normal male subjects between the ages of 26 and 46 years. During the initial phase of the study electrocardiograms recorded on direct-writing electrocardiographs at 25 mm. per second with a standardization sensitivity of 10 mm. per millivolt were used, so that measurements could be related to those used for clinical interpretation. These electrocardiograms were optically magnified 10 times for better visualization of the beginning and end of waves to obtain more precise measurements.[1] The P-R segment was measured in all 12 leads of 20 of these electrocardiograms. The P-R segment was defined as that portion of the electrocardiogram inscribed as an isoelectric line between the discernible termination of the P wave and the onset of the first deflection attributable to the ventricular complex.

Difficulty was experienced in measurement due to the usual thick baseline of tracings with the standard sensitivity of 10 mm. per millivolt. These 2 factors, regardless of instruments used, hinder detection and accurate interpretation of minor potential changes. To sharpen the points of potential change on the X axis of the electrocardiogram and for better visualization of the region of the P-R segment, a paper speed of 75 mm. per second was adequate if the electocardiograph's sensitivity was increased to a range of 250 to 500 mm. per millivolt. This could be accomplished only with cathode-ray tube electrocardiographs. The latter instruments were used during the remainder of the study for verification of the findings suggested by the optically magnified directly written electrocardiograms.

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Results

In the directly written electrocardiograms, the average duration of the P-R segment was 0.06 second. Each group of standard, augmented, or precordial leads had approximately the same average value (table 1). Although the average value of the P-R duration was 0.06 second, the minimal P-R segment in each electrocardiogram ranged from 0 to 0.06 second (table 2). The lead with the shortest P-R segment was unpredictable. Virtual nonexistence of a P-R segment was noted in tracings from 4 subjects in which the terminal limb of the P wave fused with the initial deflection of the QRS (fig. 1).

After measurements of the average duration for each lead were contrasted with the measurements of the minimal durations, it was evident that the average or the range of average duration of the P-R segment in a single or a series of electrocardiograms provides no information comparable with physiologic processes. The shortest P-R segment measurable in a given electrocardiogram is the only meaningful value.

In the tracings recorded photographically from the cathode-ray tube electrocardiographs, points of potential change were more

TABLE 1.—*The Average Duration of the P-R Segment in Twenty Normal Subjects*

Lead	1	2	3	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6
Second	.06	.06	.07	.06	.06	.06	.07	.07	.05	.05	.05	.06

TABLE 2.—*Incidence of Minimal P-R Segment Durations* in Twenty Normal Subjects*

Second	0.00	0.01	0.02	0.03	0.04	0.05	0.06
Incidence	5	3	4	6	5	2	1

* In certain instances the minimum duration appeared in 2 or more leads.

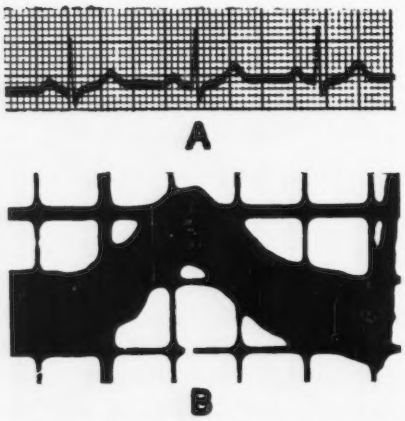

FIG. 1. *A.* Lead II from electrocardiogram of normal subject. Direct-writer tracing at 25 mm. per second and standard sensitivity. *B.* At 10 × optical magnification it is difficult to discern the presence of a P-R segment, since the slope of the terminal limb of the P wave fuses with the earliest deflection due to the Q wave.

clearly evident. During the time an isoelectric P-R segment is inscribed in the conventional electrocardiogram, a rapid but low amplitude change in potential exists (figs. 2 and 3). This abrupt change in slope of the electrocardiographic curve occurs because the direction of the onset of the wave of ventricular depolarization is opposite to that of the terminal limb of the P wave. The inscription of an isoelectric segment between the P and the QRS in the routine electrocardiogram is due to the inability of electrocardiographs to respond to rapid low-amplitude

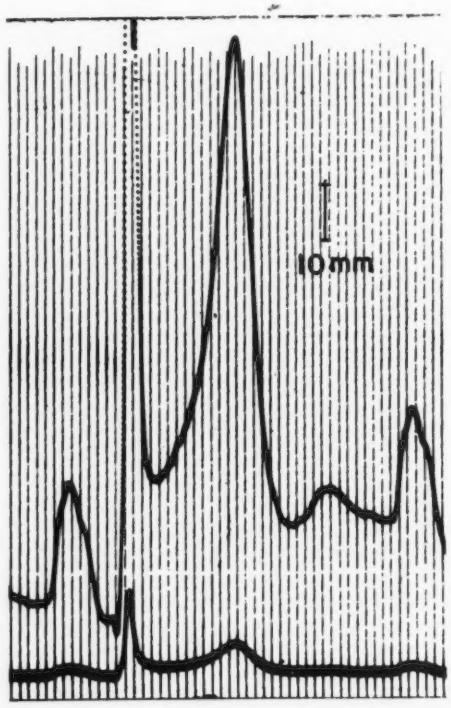

FIG. 2. Simultaneous tracings of lead II taken with cathode-ray tube electrocardiograph. Paper speed, 75 mm. per second; time lines, 0.02 second. Standardization is 10 mm. per millivolt in lower tracing and 250 mm. per millivolt in the upper tracing. There is fusion of the termination of the P wave and a slight 1 mm. upstroke preceding a minute Q wave not evident on the comparison tracing. S-T segment elevation is hardly noticed at 10 mm. per millivolt standardization; the S-T segment is shown to be the slow upstroke of the T wave. A U wave is clearly present, but not detected at the ordinary standardization.

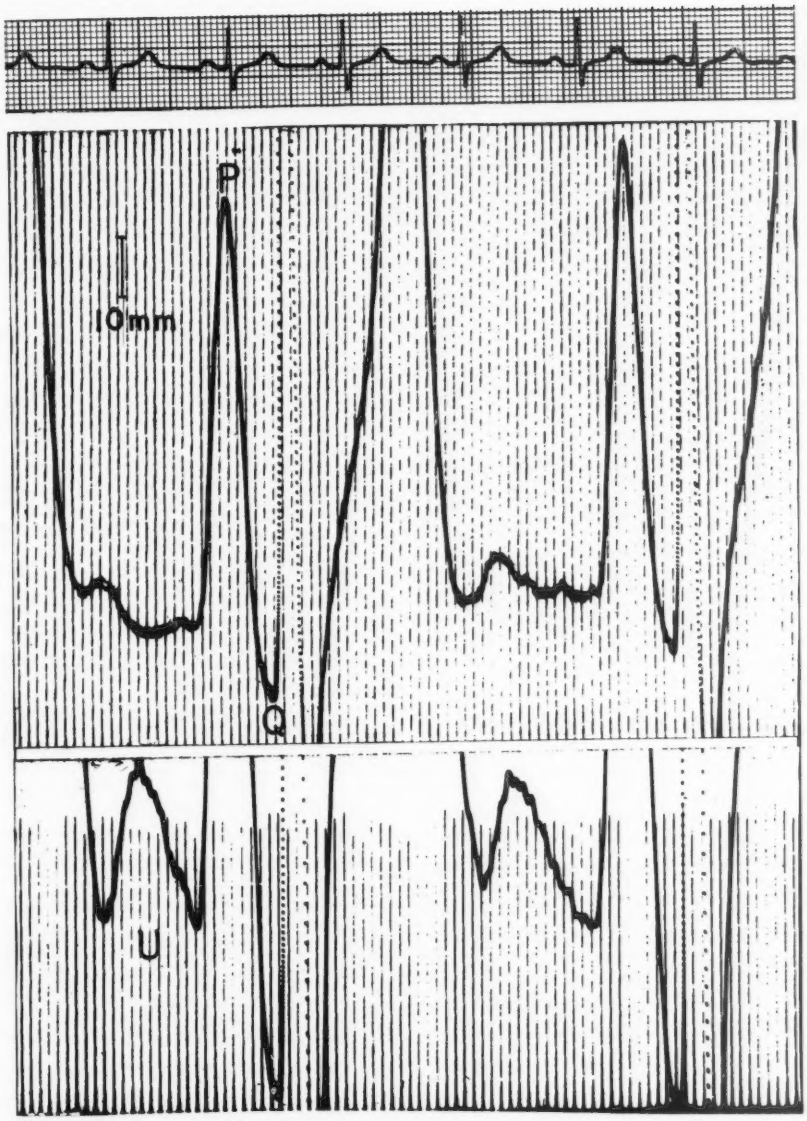

FIG. 3. Tracings are of lead II taken in succession from a normal 28-year-old man. *Upper tracing.* Standard directly written electrocardiogram with paper speed of 25 mm. per second and standardization sensitivity of 10 mm. per millivolt. *Middle tracing.* Cathode-ray tube electrocardiograph tracing recorded photographically at a paper speed of 75 mm. per second. Time lines, 0.02 second. Standardization sensitivity, 500 mm. per millivolt. Only the mid-portion of the tracing is shown. The onset and termination of the P wave are clarified and its duration can be accurately measured to be 0.13 second. The end of the P wave does not occur opposite to its onset, since the downstroke of the wave continues without change in character to meet the upstroke of the QRS. The time of the P-R segment does not exceed 0.02 second. *Lower tracing.* Approximately double the previous standardization sensitivity. Only the portion of the tracing showing sharp points of potential change is shown. The increased amplitude allows clear visualization of the junction of the downstroke of the P wave and the upstroke of the R wave. The U wave, which was undetectable at standard sensitivity, is evident.

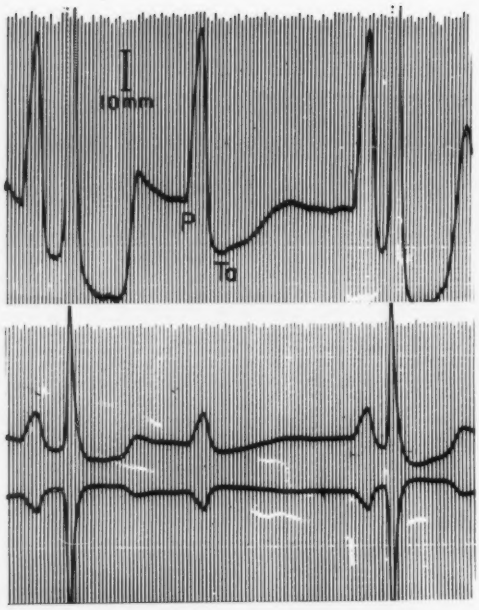

FIG. 4. *Upper tracing.* Lead II, from a patient with heart block. Atrial rate, 65 per minute. Variable ventricular rate. Paper speed, 75 mm. per second. Time lines, 0.02 second. Standardization sensitivity, approximately 500 mm. per millivolt. The configuration of the isolated P wave, and the contribution of its terminal descending limb or the potential of the P-Ta wave to the formation of the P-R segment is evident. The duration of the P wave measured from the onset of the wave to a point opposite its onset is 0.12 second. The duration from onset to the point where the terminal slope of the wave changes in character is 0.16 second. *Middle and lower tracings* are simultaneous, lead II and aV_R respectively at decreased standardization sensitivities. When precisely measured, the points of onset and termination of all waves are coincident in all leads.

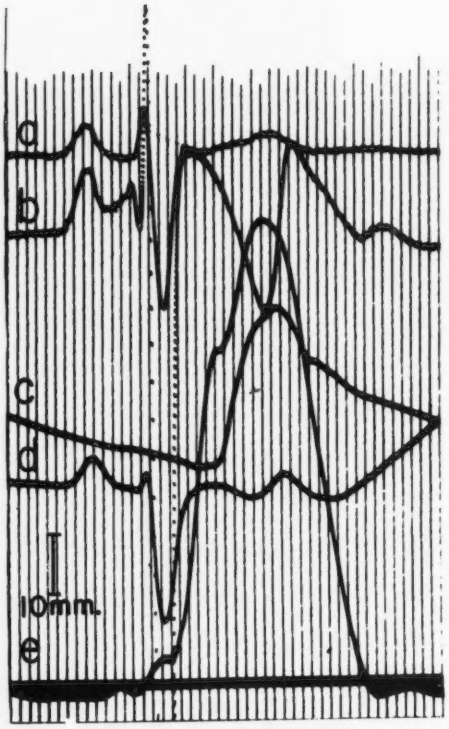

FIG. 5. Tracing obtained during cardiac catheterization of patient with pulmonary hypertension. Paper speed, 75 mm. per second. Time lines, 0.02 second. Uppermost tracing is lead I with large S wave due to right axis deviation. The second tracing is the right ventricular intracavitary lead. After inscription of the P wave in the intracavitary lead, an upstroke denoting rise in potential follows. This is not reflected in the limb lead. The simultaneous tracings below are brachial artery pulse pressure, an esophageal lead, and right ventricular pulse pressure.

potential variations because of their frequency and mechanical limitations, particularly when used with the standard sensitivity of 10 mm. per millivolt.

DISCUSSION

The importance attributable to a P-R segment is its representation of the interval of time between the end of atrial depolarization and the beginning of ventricular depolarization. Electrocardiographically that time interval may be nonexistent.

Uninterrupted visualization of the terminal slope of the P wave can be obtained only in individuals with heart block after inscription of an isolated P wave (fig. 4). When the entire terminal slope of the P wave is seen adequately, it is apparent that the portion inscribed prior to the P-Ta wave may be masked in the routine electrocardiogram, since the duration of the terminal portion of the P wave may overlap the time during which the limb lead QRS is inscribed. Similarly, ventricular potential variations are occasion-

ally recorded in intracavitary leads prior to the onset of the limb lead QRS and during limb-lead P-wave inscription (fig. 5). The close approximation of the terminal slope of the P wave and the beginning of the QRS complex within a short interval of time in routine limb-lead electrocardiograms further suggests that an isoelectric segment between P and QRS is derived from either the junction of electrical signals from the termination of atrial depolarization and the onset of ventricular depolarization or the algebraic summation of the simultaneous potential changes from these events. Detailing of each event separately or of the potential variations at their points of junction is not possible with present instrumentation.

In instances in which the potential from the terminal portion of the P wave may have ceased prior to the onset of ventricular depolarization, the P-Ta wave potential is an unsubtractable component of the wave form inscribed by the electrocardiograph during the time of ventricular depolarization. Thus, potential variation from atrial electrocardiographic activity is intimately related with potential from the initial portion of the ventricular depolarization process at points between P and QRS. Clinically, aberrations of the QRS complex, particularly of its initial portion, must be considered possibly to be due to the continuation of the relationship of the same electrophysiologic events.

Summary

Limitations in the methods of recording and limitations inherent in instrumentation account for the inscription of an isoelectric segment between the P and QRS in routine normal electrocardiograms. During its inscription rapid low-amplitude potential variations are present due to the junction or summation of atrial and ventricular waves. The sources of potential variation that influence the formation of the apparent isoelectric segment need not terminate their activity between the P and QRS and, thus, become of significance in interpretation of QRS abnormalities.

Acknowledgment

The authors acknowledge, with appreciation, the criticisms and helpful suggestions of Drs. Robert P. Grant and Clayton B. Ethridge, and the generous assistance of Drs. Irene Hsu and Harold Orvis in the preparation of this paper.

Summario in Interlingua

Limitationes del methodos registratori e limitationes inherente in le instrumentation explica le inscription de un segmento isoelectric inter le P e le QRS de normal electrocardiogrammas routinari. Durante le inscription de iste segmento, rapide variationes de potential de basse amplitude es presente como effecto del junction o del summation de undas atrial e ventricular. Le fontes del variation de potential, le quales influentia le formation del apparente segmento isoelectric non termina lor activitate necessarimente inter le P e le QRS e deveni assi un factor de signification in interpertar anormalitates de QRS.

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Effect of Prolonged Use of Estrogens on Circulating Lipids in Patients with Idiopathic Hyperlipemia or Idiopathic Hypercholesteremia

By Elaine Bossak Feldman, M.D., Chuni Wang, M.D., and David Adlersberg, M.D.

The low incidence of atherosclerosis in premenopausal women and the effects of gonadal extracts on serum lipids indicate the desirability of further clinical and biochemical studies. Ethinyl estradiol was administered to 12 persons with idiopathic hyperlipemia or idiopathic hypercholesteremia. Medication was given for an average period of 16 months and was well tolerated, despite moderate gynecomastia, diminished libido, or uterine bleeding. The effects on the levels of circulating lipids and the clinical feasibility of this therapy are discussed.

THE lower incidence of coronary atherosclerosis in premenopausal women as compared to men is well established.[1] Sex and age differences in levels of serum lipids and lipoproteins suggest an important role of the gonads in the regulation of circulating lipids.[2-5] Administration of estrogenic hormones to men and women is followed by a fall in serum lipid levels and alteration in serum lipoprotein patterns.[1, 6-9] A number of studies have been concerned with the administration of estrogens to patients with coronary artery disease.[1, 10-16]

Patients with idiopathic hyperlipemia or idiopathic hypercholesteremia provide a unique material for the study of disturbances in circulating lipids per se and in relation to lipid deposition in the tissues that often accompanies these disorders.[17] Therefore, a study was undertaken of the long-term use of orally administered ethinyl estradiol, at minimum effective doses, in men and women with either disorder. A preliminary report appeared previously.[18]

Materials and Methods

Selection of Patients. The group with idiopathic hyperlipemia included 4 men, age 39, 47, 49, and 52, and 2 women, age 49 and 56 (both postmenopausal). Four patients, 3 men and 1 woman, had xanthomata tuberosa; 1 man also had tendinous xanthomata. Other pertinent clinical data are summarized in table 1.

In the group with idiopathic hypercholesteremia, there were 3 men and 3 women. The men were age 47, 50, and 54 and the women were 47 (still menstruating), 48, and 50 years old (postmenopausal) at the inception of the study. One woman and 1 man had xanthomata tendinosa. Other clinical manifestations are noted in table 1.

The individual pretreatment levels of serum lipids and lipoproteins are presented in table 2. In the group with idiopathic hyperlipemia mean levels of total and esterified cholesterol were 579 and 384 mg. per cent; phospholipid levels averaged 647 mg. per cent, triglycerides 2,642 mg. per cent, and total lipids 3,878 mg. per cent. α-lipoprotein was 11.2 per cent, β-lipoprotein 37.1 per cent, and the O-fraction 51.7 per cent of the total stainable lipoprotein, with a β plus O : α ratio of 7.9. In the group with idiopathic hypercholesteremia the mean levels of total and esterified cholesterol were 434 and 330 mg. per cent, phospholipids 412 mg. per cent, triglycerides 452 mg. per cent and total lipid 1,298 mg. per cent. Average level of α-lipoprotein was 17.4 per cent, β-lipoprotein 65.0 per cent, and O-fraction 17.5 per cent; β plus O : α ratio was 4.7.

All patients had been observed by at least one of the investigators for a period of 1 to 5 years prior to the study. During this period of time, determinations of serum lipids and lipoproteins had been serially recorded. All patients had been maintained on a low-fat diet which was not altered throughout the course of treatment. Treatment with digitalis, diuretics, or nitroglycerin was continued as needed. No patient received any anticoagulant during the period of the study. Under the conditions of this study each patient served as his own control for at least 1 year.

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Method. Measurements followed at bimonthly or monthly intervals included body weight; stigmata of the disordered lipid metabolism such as symptoms and signs of coronary artery disease, number and size of skin and tendon lesions; fasting levels of serum total and esterified cholesterol, phospholipids, and total lipid by chemical methods (triglycerides calculated by difference)[19-21]; levels of lipoproteins (α, β, and O-fraction) and proteins (albumin, α, β, and γ globulins) by paper electrophoresis and subsequent staining with oil red O for lipids and amidoblack for proteins followed by quantitative densitometric evaluation with a Spinco Analytrol.[22-24]

Dosage of Ethinyl Estradiol. Patients were initially started on ethinyl estradiol* in dosage of 0.1 mg. twice a day which after 4 weeks was reduced to 0.05 mg. 3 times a day. If a satisfactory lipid-lowering effect was obtained, the dose was reduced to 0.05 mg. twice a day or sometimes once a day. Dosage was later altered in some patients to interrupt therapy by administering medication for 3 weeks and discontinuing it for 1 week. In 1 man with hyperlipemia and 1 man and 3 women with hypercholesteremia the course of ethinyl estradiol was interrupted for from 2 to 5 months, during which time patients were maintained on a placebo. These patients were otherwise followed in the same manner as those on the drug.

To date, 12 patients have been studied from 2 to 26 months, with an average duration of 16 months of therapy. In 3 men with hyperlipemia and 1 with hypercholesteremia the study was terminated after 2, 3, 4, and 11 months, respectively. Eight patients are still receiving treatment: all women in both groups, 1 man with hyperlipemia and 2 men with hypercholesteremia.

Results

In all patients in both groups there was a significant fall in serum total and esterified cholesterol (table 2). Phospholipid levels declined in all the hyperlipemic patients and in 4 patients with hypercholesteremia and were unchanged in 2 patients in the latter group. Triglyceride and total lipid levels fell in all except 1 patient with hypercholesteremia. In all except 1 patient with hyperlipemia the lipoprotein pattern "improved" significantly in both groups in that there was an increase in α-lipoprotein with a corresponding decrease in β-lipoprotein or the O-fraction.

*We should like to thank Dr. J. Black, of the Schering Corporation, Bloomfield, N. J. for the generous supplies of estinyl and placebo used in this study.

TABLE 1.—*Clinical Manifestations in Patients with Idiopathic Hyperlipemia or Idiopathic Hypercholesteremia Treated with Ethinyl Estradiol*

Patient	Sex	Age	Xanthoma tuberosum	Xanthoma tendinosum	Coronary artery disease	Other	Duration of therapy (months)
Hyperlipemia							
1	M	39	+				26*
2	M	47	+		+		2
3	M	49					3
4	M	52	+	+			4
5	F	49			+	Diabetes	17*
6	F	56	+		+	Pancreatitis	26*
Hypercholesteremia							
7	M	47		+			25*
8	M	50			+	Gout	11*
9	M	54			+		11
10	F	42		+	+		26*
11	F	48			+		24*
12	F	50			+		24*

*Still on therapy.

The response to and course of therapy of 1 representative patient in each group is depicted in figures 1 and 2. Levels of lipid and lipoprotein fractions are graphed in relation to therapeutic regimen over a 2-year period. Representative lipoprotein patterns for each of these patients are shown in figures 3 and 4.

The mean results in each group before and after therapy are presented in graphic form in figures 5 and 6. In the group with idiopathic hyperlipemia (fig. 5) on therapy the mean levels of total and esterified cholesterol fell by 47 and 45 per cent to 309 and 210 mg. per cent. Phospholipid levels declined by 30 per cent to 454 mg. per cent. Triglyceride levels were reduced 69 per cent to 822 mg. per cent while a 59 per cent fall occurred in total lipids to a mean level of 1,586 mg. per cent. α-lipoprotein increased to 22.0 per cent, β-lipoprotein was increased slightly to 43.1 per cent, and the O-fraction declined to 34.9 per cent of the total stainable lipid, resulting in a 56 per cent fall in the $\beta:\alpha$ lipoprotein ratio.

TABLE 2.—*Maximal Effect of Estinyl Therapy on Serum Lipids and Lipoproteins in Idiopathic Hyperlipemia or Idiopathic Hypercholesteremia*

	Patient	Total cholesterol	Esterified cholesterol	Phospholipids	Triglycerides	Total lipid	Lipoproteins α	Lipoproteins β	Lipoproteins O	β:α ratio
		mg. per 100 ml.					% of total stainable lipid			
Hyperlipemia										
1	Pretreatment	594	417	566	1260	2420	12.6	28.1	59.3	6.9
	Lowest level	242	183	410	538	1190	25.9	42.7	31.4	2.9
	Per cent fall	59	56	28	57	51				58
	Placebo	447	305	386	697	1530	9.6	50.9	39.5	9.4
2	Pretreatment	706	476	744	6440	7890	13.4	50.3	36.3	6.5
	Lowest level	468	292	584	1538	2590	27.0	22.3	50.7	2.7
	Per cent fall	34	39	22	76	67				58
3	Pretreatment	551	337	708	2466	3725	7.9	35.3	56.8	11.7
	Lowest level	425	283	536	1124	2085	14.0	60.5	25.5	6.1
	Per cent fall	23	16	24	54	45				48
4	Pretreatment	734	530	552	934	2220	11.0	27.3	61.7	8.1
	Lowest level	249	178	386	305	940	29.9	59.8	10.3	2.3
	Per cent fall	66	66	30	67	58				72
5	Pretreatment	570	337	808	3392	4770	9.5	40.6	49.9	9.5
	Lowest level	281	181	400	799	1480	18.6	38.8	42.6	4.4
	Per cent fall	51	46	50	76	69				53
6	Pretreatment	318	206	506	1421	2245	13.0	41.0	46.0	6.7
	Lowest level	192	123	410	628	1230	16.5	34.3	49.2	5.1
	Per cent fall	40	40	19	56	45				24
Hypercholesteremia										
7	Pretreatment	465	396	424	256	1145	10.6	71.2	18.2	8.4
	Lowest level	385	281	464	531	1380	38.9	38.9	23.2	1.6
	Per cent fall	17	29							81
	Placebo	544	386	464	332	1340	18.5	73.4	8.1	4.4
8	Pretreatment	346	248	372	587	1305	16.5	54.6	28.9	5.1
	Lowest level	240	163	362	208	810	44.8	37.3	17.9	1.2
	Per cent fall	31	34	3	65	38				76
9	Pretreatment	306	221	378	501	1185	32.9	45.6	21.5	2.0
	Lowest level	206	150	316	258	740	45.6	40.3	14.0	1.2
	Per cent fall	33	32	16	49	38				40
10	Pretreatment	447	330	464	764	1675	14.4	74.0	11.6	6.0
	Lowest level	323	252	372	575	1270	35.5	54.8	9.7	1.8
	Per cent fall	28	24	20	25	24				70
	Placebo	674	578	584	592	1850	16.8	78.1	5.1	5.0
11	Pretreatment	472	368	386	322	1180	15.0	67.3	17.6	5.7
	Lowest level	228	146	336	486	1050	25.0	65.0	10.0	3.0
	Per cent fall	52	60	13		11				47
	Placebo	436	311	350	474	1210	15.7	59.7	24.6	5.4
12	Pretreatment	566	418	450	284	1300	15.2	77.3	7.4	5.6
	Lowest level	314	214	360	231	905	36.1	44.9	19.0	1.8
	Per cent fall	45	49	20	19	30				68
	Placebo	523	366	386	301	1210	16.5	72.0	11.5	5.1

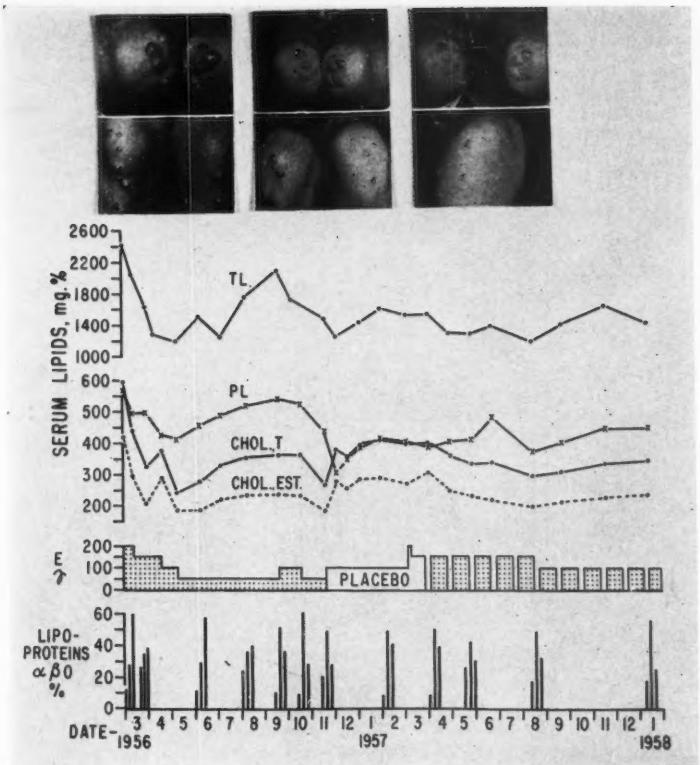

FIG. 1. Effect of prolonged estinyl therapy on skin lesions and circulating lipids in patient 1, with idiopathic hyperlipemia and xanthoma tuberosum. The upper row of photographs presents xanthomas of the elbows; the lower, those of the knees. Pictures 1 and 4 were taken prior to the institution of estinyl therapy; 2 and 5, after 7½ months; and 3 and 6, after 14 months of estinyl therapy. Low-fat diet was maintained prior to and during estinyl therapy. Note marked regression of xanthomatous lesions of elbows and knees. The changes in circulating lipids are presented in the lower part of the figure. *TL*—total lipids; *PL*—phospholipids; *Chol. T.*—total cholesterol; *Chol. Est.*—esterified cholesterol; *E*—ethinyl estradiol in mcg. per day. Serum lipoproteins are presented at the bottom of the graph; the 3 columns of each group represent α-lipoprotein (*left*), β-lipoprotein (*center*), and O-fraction (*right*).

In the group with idiopathic hypercholesteremia (fig. 6) on therapy there was a fall of 35 and 39 per cent in the mean levels of total and esterified cholesterol to 283 and 201 mg. per cent. Phospholipid levels declined 11 per cent to 368 mg. per cent. Reduction of 17 per cent occurred in triglycerides, to 375 mg. per cent and total lipid levels fell 23 per cent to a mean of 1,026 mg. per cent. α-lipoprotein increased to 37.6 per cent and β-lipoprotein fell to 46.9 per cent while the O-fraction declined slightly (15.5 per cent) resulting in a 64 per cent drop in the $\beta:\alpha$ lipoprotein ratio.

Significant declines in lipid levels were apparent after 4 weeks and maximal effects were usually noted after about 6 weeks of therapy. Efforts to lower the minimum effective maintenance dose of estinyl to below .1 mg. daily were uniformly unsuccessful. The serum lipid levels of most patients were stabilized on a regimen of .1 to .15 mg. daily for 3 weeks, with 1 week off therapy.

In all 5 patients on the placebo regimen, lipid and lipoprotein levels gradually reverted

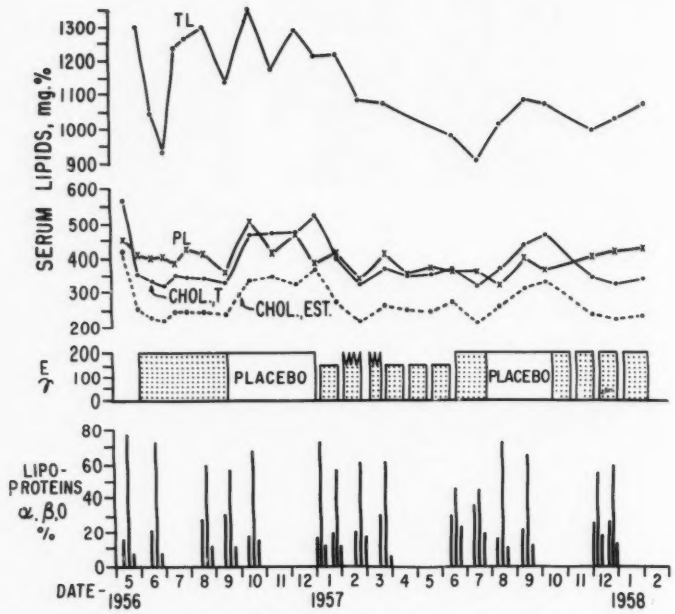

FIG. 2. Effect of prolonged estinyl therapy on circulating lipids in patient 12, with idiopathic hypercholesteremia. Legends as in figure 1.

toward pretreatment values (table 2). In 1 instance of hypercholesteremia, the levels after 7 weeks on placebo were actually higher than before therapy. The time required for reversion of the lipid levels in the other patients was 5 months in the male patient with hyperlipemia and 3 and 4 months in 2 hypercholesteremic women. The rate of increment in total cholesterol when estrogen therapy was stopped averaged 49 mg. per cent per week, ranging from 20 to 85 mg. per cent.

Side Effects. The therapy was generally well tolerated by the patients. There were no complaints of fatigue, weakness, or malaise as had been reported in other studies.[12] Weight was maintained in all instances. Three patients had occasional mild nausea. All men developed moderate gynecomastia or nipple sensitivity while the latter was noted by 2 women. Diminished libido was described by 5 men. Occasional uterine bleeding of mild degree and short duration was noted by 4 women. Institution of placebo administration was followed by return of full libido in 4 weeks in a man with hyperlipemia who had been on estrogen therapy for the preceding 8 months. In another man who stopped estinyl after 2 months, full libido returned in 3 weeks.

While on the study there was no instance of worsening of the course of coronary heart disease as manifested by angina, myocardial infarction, or of congestive heart failure. No deaths occurred during the study. In 1 hyperlipemic man with xanthomata tuberosa of knees and elbows there was almost complete disappearance of these lesions after 14 months of therapy. They began to regress after about 3 months of therapy (fig. 1).

DISCUSSION

It is apparent that the therapeutic scheme of the study, which provided for a minimal effective dose of estrogen and interrupted therapy, is suitable for the long-term management of patients with elevated levels of serum lipids. Therapy is particularly well tolerated by women. In more than half the men, sid

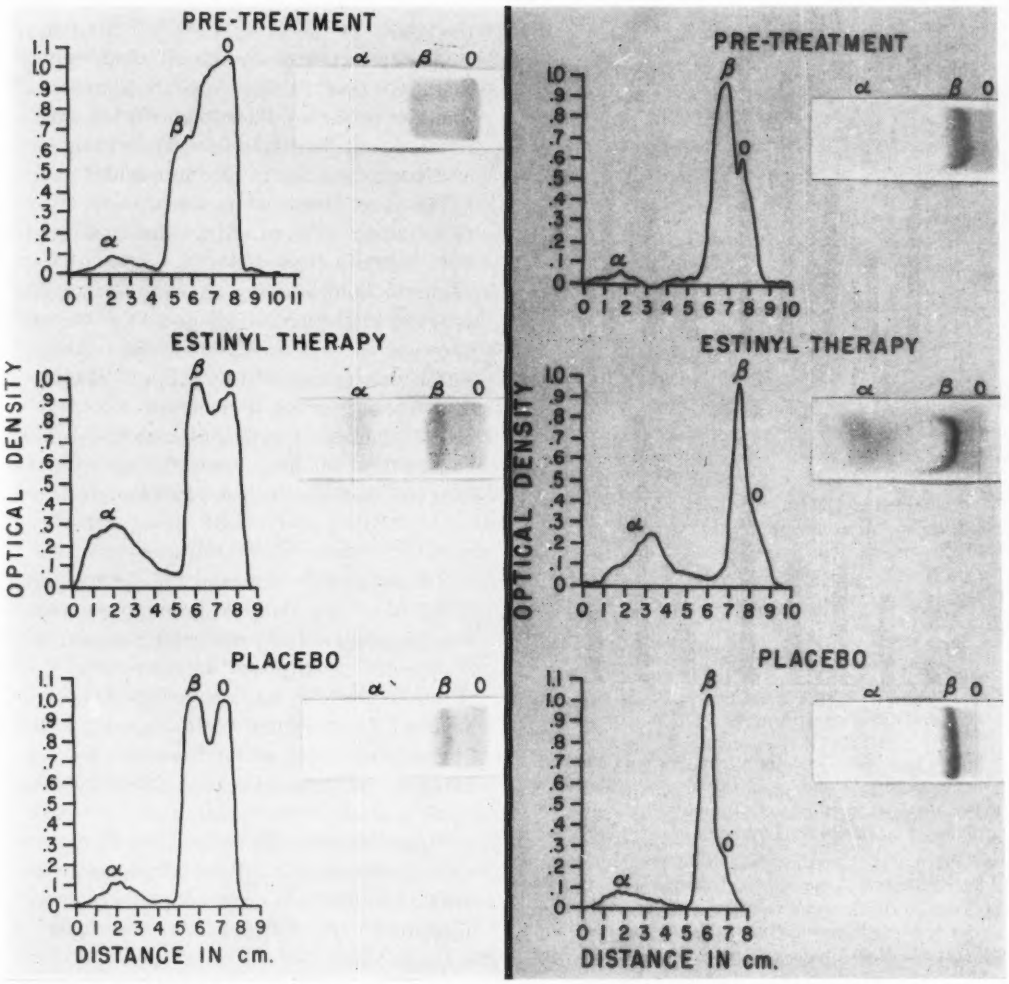

FIG. 3 *Left.* Serum lipoproteins by paper electrophoresis of patient 1 with idiopathic hyperlipemia before treatment, while on therapy with ethinyl estradiol, and on placebo. The abnormally low α-lipoprotein increased while on therapy with ethinyl estradiol and the O-fraction decreased. On placebo α-lipoprotein was again depressed. α—α-lipoprotein; β—β-lipoprotein; O—O-fraction (triglycerides adsorbed at point of origin, i.e., of application of serum).

FIG. 4 *Right.* Serum lipoproteins by paper electrophoresis of patient 12 with idiopathic hypercholesteremia, before treatment, while on therapy with ethinyl estradiol, and on placebo. Legends as in figure 3. The abnormally low α-lipoprotein fraction increased under ethinyl therapy while the β and O-fractions decreased. On placebo, there was again decided depression of α-lipoprotein.

effects were not sufficient to exclude their participation for a prolonged period of time. The effect of estrogen therapy on serum lipids and lipoproteins is constant, predictable, and continuous at a dosage range considerably lower than that employed in other studies, although still above the physiologic level even for the female.

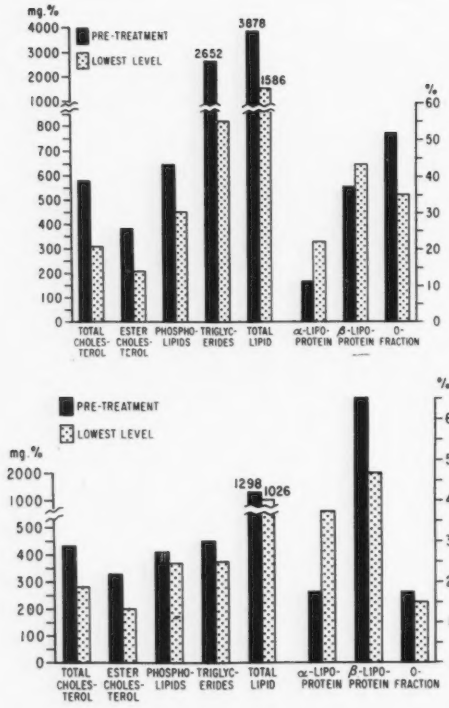

FIG. 5 *Top.* Mean levels of circulating lipid and lipoprotein fractions in group of patients with idiopathic hyperlipemia before therapy with ethinyl estradiol and at point of maximum lipid-lowering effect under treatment.

FIG. 6 *Bottom.* Mean levels of circulating lipid and lipoprotein fractions in group of patients with idiopathic hypercholesteremia before therapy and at point of maximum lipid-lowering effect under treatment with ethinyl estradiol.

Whether this type of therapy aimed at a long-term reduction of serum lipid fractions and the $\beta:\alpha$ lipoprotein ratio to approximately the normal range has any influence on the morbidity, mortality, or course of atherosclerosis, and its complications in these patients with decidedly disturbed lipid metabolism cannot be answered at present. Only prolonged observation of such patients treated with various lipid-lowering agents may provide such an answer at some future time. One external manifestation of hyperlipemia, tuberous xanthomas, was seen to disappear during the course of the present study. Similar results were reported by others using estrogen therapy,[13] and in our laboratory as a concomitant of the lipid-lowering effect of marked restriction of fat intake, after thyroid therapy, or after large doses of nicotinic acid.[25]

The use of hormonal agents provides a practical means of controlling abnormal serum lipid and lipoprotein levels. Such therapy might be improved by the use of synthetic estrogen analogues which preserve the lipid-lowering effect and eliminate the feminizing action in a moderate dose range.[26] Studies of this sort, in progress in numerous laboratories, may lead to more definitive measures for the management of disturbances in lipid metabolism and, perhaps their clinical complications.

SUMMARY

Ethinyl estradiol in minimal effective doses of 0.2 to 0.1 mg. daily in interrupted courses was administered to 7 men and 5 women with idiopathic hyperlipemia or idiopathic hypercholesteremia for an average period of 16 months. In the group with idiopathic hyperlipemia mean levels of total and esterified cholesterol, phospholipids, triglycerides, and total lipids fell 30 to 69 per cent from pretreatment values. There was an increase in α-lipoprotein and a fall in β-lipoprotein and the $\beta:\alpha$ lipoprotein ratio. In the group with idiopathic hypercholesteremia mean levels of lipid fractions fell 11 to 39 per cent from pretreatment values. α-lipoprotein increased and β-lipoprotein and the $\beta:\alpha$ lipoprotein ratio decreased. A return toward pretreatment values within 2 to 5 months occurred in 5 patients placed on a placebo regimen.

Therapy was well tolerated. Side effects included moderate gynecomastia, sensitive nipples, diminished libido, and uterine bleeding. Almost complete disappearance of extensive xanthomata tuberosa occurred in 1 man with idiopathic hyperlipemia after 14 months of therapy.

The use of ethinyl estradiol provides a practical means of controlling abnormal serum lipid and lipoprotein levels.

SUMMARIO IN INTERLINGUA

Estradiol ethinylic in doses minime efficace de 0,2 a 0,1 mg per die in cursos interrumpite esseva administrate a 7 masculos e 5 femininas con hyperlipemia idiopathic o con hypercholesterolemia idiopathic durante un periodo medie de 16 menses. In le gruppo con hyperlipemia idiopathic, le nivellos medie de cholesterol total e esterificate, de phospholipidos, de triglyceridos, e de lipidos total descendeva per 30 a 69 pro cento del valores pretractamental. Esseva constatate un augmento de lipoproteina alpha e reductiones del lipoproteina beta e del proportion de lipoproteina beta a lipoproteina alpha. In le gruppo con hypercholesterolemia idiopathic, le nivellos medie del fractiones lipidic descendeva per 11 a 39 pro cento del valores pretractamental. Lipoproteina alpha se augmentava e lipoproteina beta e le proportion de lipoproteina beta a lipoproteina alpha se reduceva. Un retorno al valores pretractamental occurreva intra 2 a 5 menses in 5 patientes recipiente un medication fictitie.

Le therapia esseva ben tolerate. Le effectos lateral includeva grados moderate de gynecomastia, sensibilitate del papillas, regression del libido, e sanguination uterin. Le disparition quasi complete de extense xanthomas tunerose occurreva in 1 masculo con hyperlipemia idiopathic post 14 menses de therapia.

Le uso de estradiol ethinylic representa un medio practic pro regular anormal nivellos de lipido e lipoproteina in le sero.

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There are 3 main types of atrial septal defects, any of which may be associated with anomalous pulmonary venous drainage. They are the high defect or sinus venous type, the fossa ovalis or ostium secundum defect, and the ostium primum defect. The volume of the shunt is the chief surgical indication. The authors considered pronounced elevation of the pulmonary vascular resistance as a contraindication to surgery. The electrocardiogram should show right ventricular hypertrophy and right axis deviation. A tendency to left axis deviation may suggest an ostium primum defect. The reported surgical experience in this series is 49 patients—46 secundum defects, 2 primum defects, and 1 sinus venous defect. The basic surgical approach was described and emphasis was placed on the importance of a well-trained surgical team. Four operative deaths occurred in the first 10 patients and in none thereafter. Open-heart surgery was used in combination with hypothermia. All survivors were symptomatically improved.

Krause

Hemodynamic Sequelae of Sustained Elevation of Left Atrial Pressure

By Arthur Selzer, M.D.

A comparison of hemodynamic findings in 63 cases of mitral stenosis and in 35 cases of chronic left ventricular failure is presented. It is shown that circulatory dynamics of the 2 conditions are similar and only minor differences were detected.

SIMILARITIES between mitral stenosis and left ventricular failure, regarding their effects upon the pulmonary circulation and the right heart, have been known long before cardiac catheterization permitted their direct assessment. The advent of mitral valve surgery, a decade ago, stimulated widespread interest in the hemodynamics of mitral stenosis. On the other hand, circulatory changes associated with cardiac failure have been studied in considerably less detail. In 1955, Harvey et al.[1] raised an important practical point regarding this similarity: are hemodynamic changes caused by mechanical factors (mitral stenosis) and those caused by myocardial factors (cardiac failure) distinctive enough to permit their differentiation? These authors answered this question in the affirmative, suggesting that venous catheterization of the heart is helpful in the selection of proper candidates for surgical treatment. The purely surgical aspect of this problem can now be approached in a more direct way, in that combined right and left heart catheterization permits the direct measurement of the diastolic gradient across the mitral valve. Other aspects of the similarity and dissimilarity between mitral stenosis and left ventricular failure are, however, of considerable importance, particularly in view of the increasing interest in the mechanism of pulmonary hypertension which may complicate these conditions. The current study was undertaken in an effort to compare circulatory dynamics of these 2 conditions in a larger series of cases, and to present them quantitatively by taking into consideration their respective severity.

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Supported by a grant from the San Mateo County Heart Association.

Material and Methods

The material for this study consisted of 63 cases of mitral stenosis and 35 cases of left ventricular failure, a total of 98 cases. All patients underwent a detailed clinical scrutiny, and the diagnosis was established on the basis of clinical, electrocardiographic, phonocardiographic, and radiologic examinations. The group of cases with mitral stenosis included patients with pure mitral stenosis and those patients with combined mitral stenosis and insufficiency in whom mitral stenosis was considered the predominant lesion. All patients thus were "surgical" cases and in most of them mitral block was severe enough to subject them to mitral valvotomy. Patients underwent cardiac catheterization at the time of a stable clinical condition; those who entered the hospital in cardiac failure, with pulmonary edema, or with uncontrolled atrial fibrillation were studied only after these complications were eliminated or brought under complete control.

Patients with left ventricular failure were selected out of a larger group of patients with low-output cardiac failure,[2] who, studied at the time cardiac failure was brought under control, showed significant elevation of left atrial pressure (pulmonary wedge pressure over 15 mm. Hg). The clinical diagnoses included hypertensive heart disease, arteriosclerotic (coronary) heart disease, and aortic valvular disease.

Cardiac catheterization was performed according to uniform standards used in this laboratory.[3, 4] The mode of study, the technic of recording pressures, the method for the study of cardiac output, and the exercise load have all been carefully standardized so as to make the findings comparable.

Results

In order to assess properly the hemodynamic effects of mitral stenosis and of chronic left ventricular failure it was necessary to find

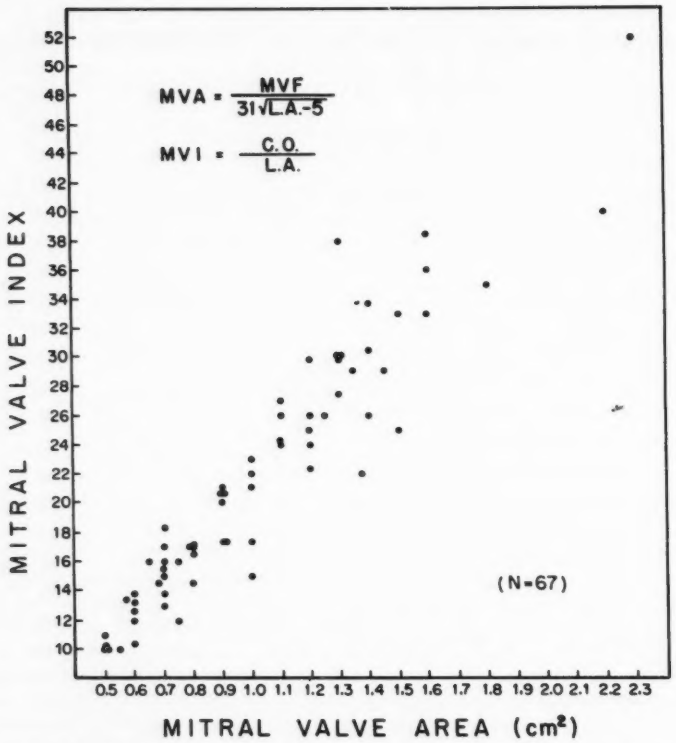

FIG. 1. Relationship between the CO/LAP ("mitral valve") index and the calculated mitral valve area in 67 cases of mitral stenosis.

means of making the severity of each condition comparable with each other. The immediate effect of mitral block and of left ventricular failure, the elevation of left atrial pressure, is in itself not an adequate yardstick of severity of each condition because of its dependence upon the magnitude of cardiac output. It was therefore considered that a ratio of cardiac output to left atrial pressure would be a more desirable indication of the severity of the circulatory derangement. This ratio has been first used by Wood[5] as a simplified substitute for the calculation of the mitral valve area, and is derived from the formula

$$\frac{\textit{cardiac output (L./min.)}}{\textit{pulmonary wedge pressure (mm. Hg)}} \times 100$$

CO/LAP index, and is termed "mitral valve index." Actually, this index does not take into consideration the gradient across the mitral valve in diastole and therefore more properly expresses the resistance to diastolic filling of the left ventricle, being applicable equally well to left ventricular failure as to mitral stenosis, because it is immaterial whether this resistance is caused by mechanical obstruction or by incomplete emptying of the failing ventricle. In order to assess the value of this index in expressing the severity of mitral stenosis, it was compared with the mitral valve area (MVA) calculated from the formula of Gorlin and Gorlin[6] in the series of 67 cases of mitral stenosis. This comparison (fig. 1) shows an excellent correlation. As suggested by Wood,[5] severe mitral stenosis is shown by an index less than 15 (MVA less than 0.75 cm.^{2}); moderate mitral stenosis by an index between 15 and 25 (MVA 0.75 to 1.25 cm.^{2}); mild mitral stenosis by an index more than 25. Obviously, mild, moderate, and severe left

TABLE 1.—*Summary of Hemodynamic Findings in More Severe Cases of Mitral Stenosis and of Chronic Left Ventricular Failure (Index 8 to 15)*

	Age	CO/LAP index	Pulmonary wedge pressure (mm. Hg)	Pulmonary arterial pressure (mm. Hg)	Pulmonary arterial pressure exercise (mm. Hg)	Cardiac output, rest (L./min./M.²)	Cardiac output, exercise (L./min./M.²)	Pulmonary vascular resistance (dynes sec. cm.⁻⁵)
Mitral stenosis (19 cases)								
Mean value	40	12.1	31.4	56.2	76.6 (36% increase)	2.1	2.5 (19% increase)	533
Range	18-61	10-15	17-40	25-79	32-106	1.7-2.7	1.8-3.6	75-1050
Left ventricular failure (15 cases)								
Mean value	50.7	10.5	29.2	45.1	62.5 (45% increase)	1.7	2.0 (18% increase)	513
Range	55-65	8-13.5	16-36	30-74	43-90	1.2-3.6	1.5-2.6	110-1020

ventricular failure can be graded by a similar range of indices.

The material was divided into 2 groups reflecting the severity of mitral stenosis and left ventricular failure respectively, with the dividing line set arbitrarily at index of 16. Group I included cases of severe mitral stenosis and severe left ventricular failure with indices from 8 to 15. The second group included all other cases, the index being over 15. Table 1 presents a summary of the findings, showing the mean values and the ranges of the various hemodynamic measurements in group I. It is seen that the mean age of patients with left ventricular failure is higher and the mean value for the index slightly lower in left ventricular failure than in mitral stenosis. The mean value for left atrial pressure is similar in the 2 groups. Pulmonary artery pressure is slightly higher in mitral stenosis, both at rest and during exercise, although the per cent increase with exercise is not materially different in the 2 groups. The cardiac output is abnormally low in both groups and appears to be lower in the patients with cardiac failure than in those with mitral stenosis. However, the per cent increase of the output with exercise is identical in both groups, being abnormally low in both. Pulmonary vascular resistance is abnormally high in both groups, the mean values being elevated to the same extent.

Table 2 shows a summary of findings in the milder cases of mitral stenosis and of left ventricular failure. Here, the mean value for the index is similar in both classes. The age shows an even wider spread than in severe cases. Pulmonary wedge and resting pulmonary arterial pressure are similar in both classes and the increase with exercise, which is abnormal in both, is more marked in left ventricular failure. The mean resting cardiac output is slightly below normal in mitral stenosis, and is still lower in cardiac failure. There is, however, an appreciable difference in its response to exercise: the increase in output in mitral stenosis is normal, while in cardiac failure it is abnormally low. Pulmonary vascular resistance is at the upper limit of normal in mitral stenosis, but is abnormally elevated in left ventricular failure, where the mean value is twice that of the other group. The 2 most important hemodynamic findings, the resting cardiac output and the pulmonary vascular resistance are compared in the 2 classes in figures 2 and 3. Figure 2 shows the relationship between the resting cardiac output and the severity of mitral stenosis and left ventricular failure, respectively, expressed as the CO/LAP index. It is seen that a normal cardiac output (shaded area) is found, as a rule, in both conditions with indices larger than 26. In severe cases, cardiac output is abnormally

TABLE 2.—*Summary of Hemodynamic Findings in Milder Cases of Mitral Stenosis and of Chronic Left Ventricular Failure (Index Over 15)*

	Age	CO/LAP index	Pulmonary wedge pressure (mm. Hg)	Pulmonary arterial pressure rest (mm. Hg)	Pulmonary arterial pressure exercise (mm. Hg)	Cardiac output, rest (L./min./M.²)	Cardiac output, exercise (L./min./M.²)	Pulmonary vascular resistance
Mitral stenosis (43 cases)								
Mean value	40.5	23	21.5	31.4	44.3 (40% increase)	2.5	3.7 (47% increase)	159
Range	28-56	16-35	16-27	21-54	25-72	2.0-3.1	2.6-5.2	60-385
Left ventricular failure (18 cases)								
Mean value	61.9	22.9	19.3	33.4	51.7 (55% increase)	2.3	2.7 (18% increase)	266
Range	44-74	16-35	15-24	21-57	36-75	1.7-3.2	1.7-4.3	125-800

low in both conditions, but in the intermediate group of severity of 15 to 25, an abnormally low cardiac output is found more frequently in cardiac failure than in mitral stenosis.

Figure 3 shows pulmonary vascular resistance in mitral stenosis and in left ventricular failure plotted against the severity index. It is seen that abnormally high pulmonary vascular resistance is found only in moderately severe and severe cases of both conditions. It is also seen that in both conditions, an appreciable number of severe cases is found with normal or near-normal vascular resistance.

DISCUSSION

The object of this study was a comparison between the hemodynamic effects of mitral stenosis and of chronic left ventricular failure. Both these conditions have one common denominator: the sustained elevation of left atrial pressure.

The dynamics of mitral stenosis is well known. The series of cases included in this study represents a wide spectrum of severity of mitral valve block with hemodynamic findings similar to those of earlier investigators.[7-10] In mitral stenosis, elevation of left atrial pressure is caused by valvular obstruction introducing resistance to flow through the mitral orifice. The level of left atrial pressure is thus an index of the severity of mitral stenosis for a given level of flow through the orifice in diastole. Chronic left atrial hypertension is an essential and constant feature of significant mitral stenosis.

In left ventricular failure, elevation of left atrial pressure reflects resistance to diastolic filling of the incompetent left ventricle and can be considered a physiologic adaptation, permitting the overloaded and overstretched left ventricle to maintain the necessary forward flow. This may be an acute response to temporary overload, such as during exercise, when it is reversible with cessation of exercise. Furthermore, it may be a more chronic finding as an expression of left ventricular failure at rest, but still reversible by cardiac therapy. Finally it may assume the form of irreversible, chronic left ventricular failure. The frequent occurrence of chronic left ventricular failure has been shown in another study from this laboratory.[2] The series of cases of left ventricular failure included in this study falls into the last category.

In both mitral stenosis and chronic left ventricular failure, the abnormally high value for left atrial pressure expresses the severity of the circulatory disturbance only in relation to the magnitude of the cardiac output; hence the index CO/LAP was used as a more accurate expression of the degree of mitral valve

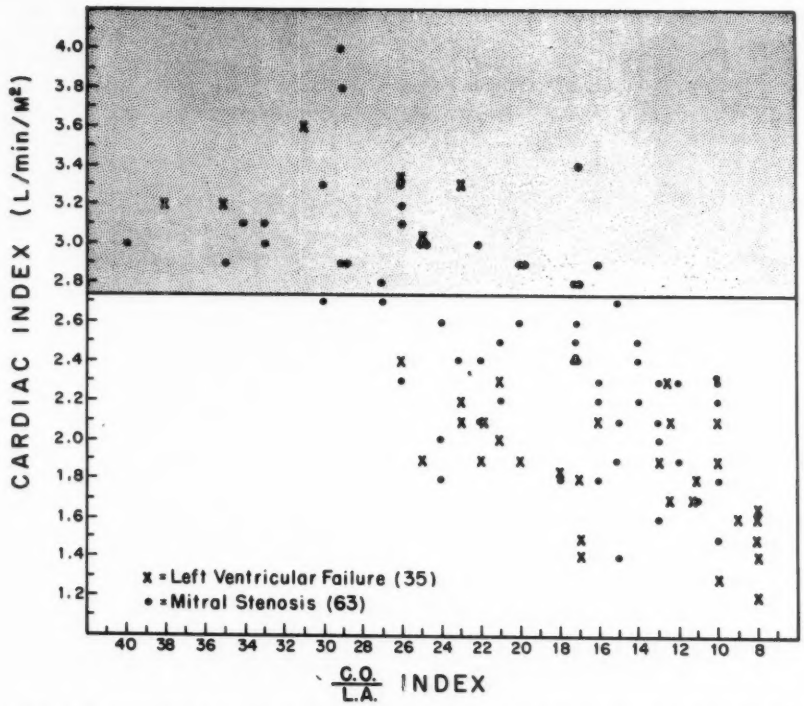

FIG. 2. Relationship between the severity of resistance in left ventricular diastolic filling, expressed as the CO/LAP index, and the resting cardiac output in patients with mitral stenosis and in those with chronic left ventricular failure. Normal zone shown as *shaded* area (above the line).

obstruction and of severity of left ventricular failure, in preference to the level of left atrial pressure alone.

From the data presented here it can be concluded that a comparison of the hemodynamic effects of mitral stenosis and of left ventricular failure reveals predominant similarities. In both these conditions, pulmonary hypertension is the rule, either passively reflecting left atrial hypertension, or exaggerated by increased pulmonary vascular resistance. Severely elevated pulmonary vascular resistance, exceeding 600 dynes sec. cm.$^{-5}$, appears as an occasional complication of severe mitral stenosis and, to a comparable extent, of severe left ventricular failure. The effect of sustained elevation of left atrial pressure upon the cardiac output is variable. In the more severe cases of mitral stenosis and of left ventricular failure alike, the resting cardiac output is almost always reduced. In both conditions, the rise of the cardiac output in response to exercise is subnormal, but most cases showed some increase, so that a "fixed" cardiac output was uncommon in this series. In milder cases, the resting cardiac output was at the low normal range, showing no difference between the 2 conditions.

Only 2 points could be noted in which the 2 conditions differed from each other: (a) significant increase in pulmonary vascular resistance was observed only in severe mitral stenosis, but occurred occasionally in milder cases of left ventricular failure (fig. 3) and by the higher mean value for pulmonary vascular resistance in milder cases of left ventricular failure versus mitral stenosis (table 2); (b) in milder cases of mitral stenosis, cardiac

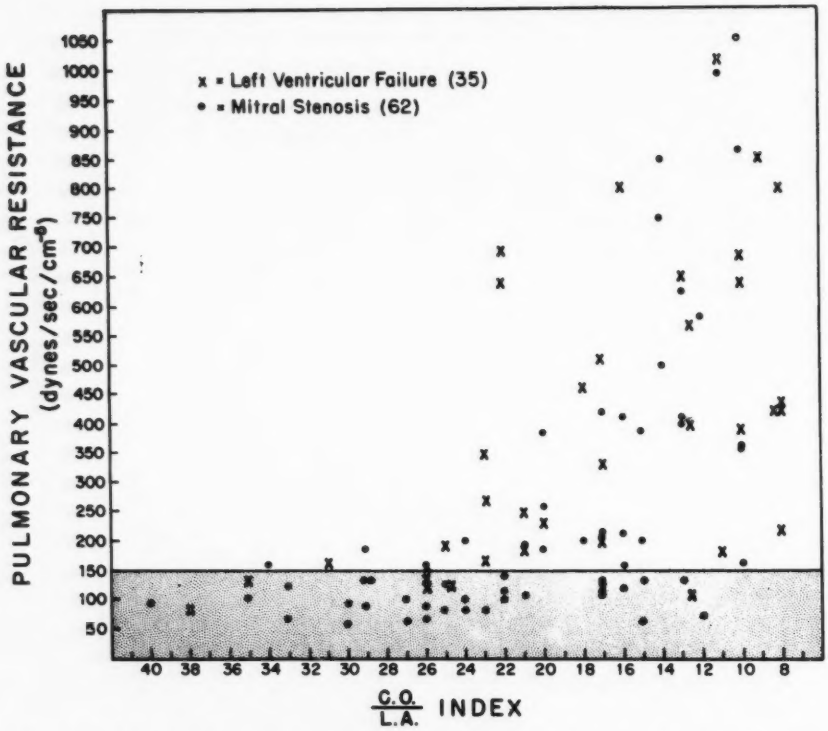

FIG. 3. Relationship between the severity of resistance to left ventricular diastolic filling, expressed as the CO/LAP index, and the pulmonary vascular resistance in patients with mitral stenosis and those with chronic left ventricular failure. Normal zone shown as *shaded* area (below the line).

output showed a normal rise with exercise, but in mild left ventricular failure this response was subnormal (table 2).

Harvey and her associates[1] reported 8 cases of mitral stenosis and an equal number of cases of cardiac failure imitating mitral stenosis, stressing the importance of pulmonary hypertension in distinguishing between mitral block and myocardial weakness. However, the arguments of these authors are subject to criticism for the following reasons: (a) their series of cases was too small to draw definitive conclusions; (b) failure to show improvement after mitral valvotomy was considered to be proof of myocardial insufficiency; (c) left atrial pressures were not measured, whereby passive pulmonary hypertension could not be distinguished from that caused by elevated pulmonary vascular resistance.

Results of this study indicate clearly that pulmonary hypertension cannot be considered a feature helpful in separating mitral block from myocardial insufficiency, because its occurrence and severity appear to be similar in the 2 conditions. In general, it is shown here that sustained elevation of left atrial pressure due to mechanical block at the mitral valve is not associated with a distinctive hemodynamic pattern, inasmuch as all the hemodynamic abnormalities caused by it occur also in chronic left ventricular failure. The differences between the 2 conditions can only be considered minor, in view of the overwhelming similarity of all the findings. These differences, furthermore, are not helpful in evaluating

individual cases because of the wide overlapping of the findings in them.

Finally, it is necessary to take into consideration the appreciable higher age of patients in cardiac failure than those with mitral stenosis, so that the observed differences may altogether be caused by circulatory responses in different age groups rather than by differences between mechanical versus myocardial factors.

Summary

A series of 98 cases, consisting of 63 patients with mitral stenosis and 35 patients with chronic left ventricular failure, was examined in order to compare hemodynamic findings in these 2 conditions. Cardiac catheterization was performed at the time when all acute complications and reversible factors were eliminated. Both mitral stenosis and left ventricular failure were graded as to the severity of the respective conditions with the use of an index:

$$\frac{\textit{Cardiac output}}{\textit{Left atrial pressure}} \times 100.$$

The hemodynamic sequelae of the sustained elevation of the left atrial pressure, which is the common denominator of mitral stenosis and left ventricular failure, showed important similarities and minor differences. It was found in both groups that pulmonary arterial pressure is always elevated, but in many cases pulmonary hypertension is severe, out of proportion to left atrial hypertension, signifying abnormally high pulmonary vascular resistance. Such cases of severe pulmonary hypertension are found in more severe cases of mitral stenosis and of left ventricular failure, and its occurrence is not appreciably different in the 2 conditions. In both conditions, the resting cardiac output is, on the average, abnormally low in severe cases and normal or slightly reduced in milder cases. Inadequate rise of cardiac output with exercise is frequently observed in both groups.

On the basis of the overwhelming similarities and relatively minor differences observed in hemodynamic changes caused by chronic elevation of left atrial pressure in mitral stenosis on the one hand, and left ventricular failure on the other hand, it is concluded that mitral stenosis does not have a distinctive hemodynamic pattern that would permit a distinction between a "mechanical block" and a "myocardial factor" unless direct measurement of left atrial and left ventricular pressure permits the demonstration of a diastolic gradient across the mitral valve.

Summario in Interlingua

Novanta-octo patientes — 63 con stenosis mitral e 35 con chronic disfallimento sinistro-ventricular—esseva examinate con le objectivo de comparar le constatationes hemodynamic in le duo mentionate conditiones. Catheterisation cardiac esseva effectuate al tempore quando omne complicationes acute e omne reversibile signos e symptomas esseva eliminate. Ambe le conditiones—stenosis mitral e disfallimento sinistro-atrial—esseva graduate secundo lor severitate in le casos individual per medio del indice:

$$\frac{\textit{rendimento cardiac}}{\textit{tension sinistro-atrial}} \times 100.$$

Le sequellas hemodynamic del prolongate elevation del tension sinistro-atrial (le qual es le characteristica commun de stenosis mitral e disfallimento sinistro-ventricular) esseva simile in importante respectos e differente in minores. Esseva constatate in ambe gruppos que le tension pulmono-arterial es semper elevate. Tamen, in multe casos iste hypertension pulmonar ha un grado de severitate foras de proportion con le hypertension sinistro-atrial, un facto que significa le presentia de un anormalmente alte resistentia pulmono-vascular. Le indicentia de un tal sever forma de hypertension pulmonar es plus alte inter le casos de sever stenosis mitral e de sever disfallimento sinistro-ventricular, sed illo non differe appreciabilemente inter le duo conditiones. In ambes, le rendimento cardiac medie in stato de reposo es anormalmente basse in casos sever e normal o pauco reducite in casos leve. Un inadequate augmento del rendimento cardiac post exercitio physic es observate frequentemente in ambe gruppos.

Super le base del frappante similaritates e del relativemente leve differentias observate in le alterationes del stato hemodynamic que es sausate per le elevation chronic del tension sinistro-atrial in (de un latere) stenosis mitral e (del altere) disfallimento sinistro-ventricular, le conclusion es formulate que stenosis mitral non se distingue per un specific configuration hemodynamic que permitterea un distinction inter "bloco mechanic" e le presentia de un "factor myocardial," excepte si le directe mesuration del tension sinistro-atrial e del tension sinistro-ventricular permitte le demonstration de un gradiente diastolic a transverso le valvula mitral.

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Cardiac Aneurysm with Ventricular Tachycardia and Subsequent Excision of Aneurysm

Case Report

By O. A. Couch, Jr., M.D.

With the introduction of ventriculoplasty the importance of diagnosis of ventricular aneurysm has increased.[1, 2] Prior to operation the subject of the following case report had episodes of ventricular tachycardia controlled with difficulty by continuous quinidine administration. Following excision of the ventricular aneurysm there were no further episodes despite the omission of quinidine.

Report of Case

The patient was first seen in September 1953 at the age of 54, when she described short abrupt spells of fluttering of the heart of 3 years' duration. She had known high blood pressure for 10 years.

Physical examination at this time revealed moderate obesity and a blood pressure of 190/110 mm. Hg. The heart and lungs were normal on examination, an electrocardiogram showed minimal ST and T-wave changes, and the heart was of normal size on chest x-ray. The patient was given rauwolfia, and her blood pressure dropped gradually to 150/80.

In April 1955, after occasional anginal pains, she suffered more prolonged pain and she was hospitalized for over 1 month with an extensive acute anterior wall myocardial infarction. The heart sounds were distant and somewhat muffled, and a protodiastolic gallop was heard. The blood pressure was 120/80. X-ray showed definite left ventricular enlargement with a convexity bulging outwardly along the upper portion of the left ventricle suggesting a ventricular aneurysm (fig. 1). The pulsations were of poor quality. Salt was restricted, the patient was digitalized, and she was also given reserpine.

Following discharge she had premature beats which persisted despite quinidine and procaine amide. On September 30, 1955, she was still weak, described one episode of nocturnal dyspnea, and showed a trace of pedal edema. An electrocardiogram in November (fig. 2) showed signs of previous infarction and ST-segment deviations consistent with aneurysm. In December she had several episodes of paroxysmal tachycardia, one of which lasted 12 hours; an electrocardiogram showed it to be ventricular in origin (fig. 2).

Physical examination showed the heart rate to be 140 and regular. The liver was felt 2 fingerbreadths below the costal margin but was smooth and nontender and there was no other sign of failure. Quinidine sulfate was started at 0.4 Gm. every 4 hours and subsequently increased to 0.6 Gm. every 4 hours. The patient reverted to a regular rhythm on the second hospital day. The dosage of quinidine was then lowered to 0.4 Gm. every 4 hours but she again developed ventricular tachycardia, this time associated with acute pulmonary edema. She was given 0.6 Gm. of quinidine every 4 hours and the rhythm again reverted to normal. The QRS interval became prolonged and the quinidine dosage was again reduced to 0.4 Gm. every 4 hours. On the ninth hospital day, however, she again developed ventricular tachycardia. She was given 0.5 Gm. of quinidine sulfate every 4 hours with a rapid return to normal sinus rhythm. She was discharged on this dosage and on 0.375 mg. of digoxin daily.

Following discharge the patient got along well except for one episode of rapid heart action that had a sudden onset but gradual cessation. She seemed to reach a plateau with very little improvement. Because of this lack of improvement and because of the difficult prospect of continuing quinidine dosage around the clock indefinitely, surgical therapy was considered. She was referred to Dr. Charles P. Bailey, of Philadelphia. The presence of the aneurysm was confirmed by roentgenkymography and left cardiac atriography.

Ventriculoplasty was carried out on April 3, 1956.[1, 2] During induction of anesthesia cardiac arrest occurred and was successfully treated with cardiac massage. Otherwise the procedure was uneventful. Postoperatively a gallop rhythm was heard for a few days and heart failure developed, but it was successfully treated. Heparin and Dicumarol were also used. Two weeks after surgery

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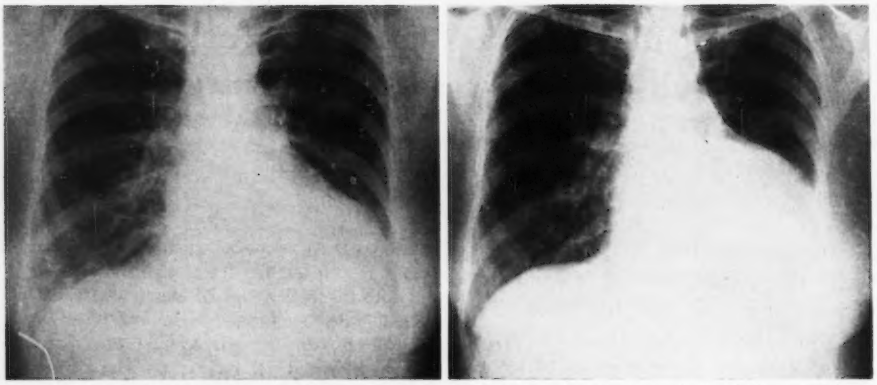

FIG. 1. *Left.* Chest film showing a bulge in the region of the apex of the left ventricle. *Right.* Postoperative film.

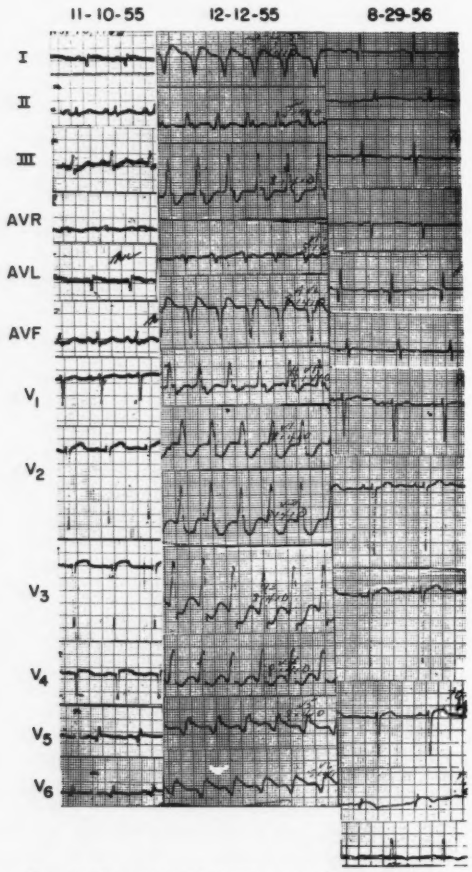

FIG. 2. November 10, 1955, postinfarction with persistent ST-segment changes attributed to aneurysm. December 12, 1955, ventricular tachycardia. August 29, 1956, postventriculoplasty.

the patient was permitted out of bed in a chair and was gradually ambulated during succeeding days.

On May 26, 1956, physical examination showed an increase in the pulmonic second sound and a loud systolic pulmonic murmur. The left border of heart dullness was still at the anterior axillary line. The lungs were clear. Fluoroscopy showed poor cardiac pulsation. An x-ray of the chest (fig. 1) showed moderate pleural reaction at the left base and disappearance of the previously described hump in the left heart border. The heart was approximately the same size but was a little more globular and not quite so prominent in the apical region.

On August 27, 1956, she was hospitalized because of mild constricting chest pain. Examination of the heart was unchanged. The white blood cell count and sedimentation rates showed moderate elevations. There were minor electrocardiographic changes but none was diagnostic of infarction. However, it was thought that the patient had probably sustained a myocardial infarction or coronary insufficiency. She was therefore started on long-term Dicumarol therapy with satisfactory maintenance of the prothrombin time within therapeutic levels. Because of a blood pressure elevation of 160/100 mm. Hg rauwolfia was given and the pressure promptly returned to normal; her heart rate also slowed considerably. She has shown no evidence of congestive failure and has been able to increase her activity over that which was possible preoperatively.

DISCUSSION

Only a few cases of ventricular tachycardia in association with ventricular aneurysm have been reported. In 1953 Wasserman and Yules[3] reported a case of a 67-year-old man

in whom an effort to control the tachycardia with intravenous and oral procaine amide was not successful. Conversion to a normal sinus rhythm was accomplished by the administration of quinidine but death occurred 3 hours later. In 1954 Walker and Richmond[4] described a case with a posterior ventricular aneurysm in a patient with dextrocardia and situs inversus. While in the hospital the patient developed paroxysmal ventricular tachycardia that was treated successfully with quinidine. No statement was made whether continuation of the quinidine was necessary to maintain the normal sinus rhythm. Dick[5] in 1955 mentioned a 59-year-old man with a posterior ventricular wall aneurysm who was seen with an episode of ventricular tachycardia. No statement was made regarding treatment.

In the present case the ventricular tachycardia was controlled only with rather exactly regulated doses of quinidine sulfate. This drug was continued until the time of operation. Following the operation the quinidine was discontinued without further recurrence of the ventricular tachycardia. This sequence suggests that an irritable focus causing the tachycardia had been removed with the removal of the ventricular aneurysm. Despite the cardiac arrest at the time of operation the patient's postoperative recovery has been excellent. She has gained strength progressively and has reached a considerably higher level of activity than was possible prior to operation. Because of an episode of chest pain that probably represented an infarct or an episode of coronary insufficiency permanent anticoagulant therapy was started. Although she has shown no evidence of congestive failure, the preoperative dosage of digoxin has been continued.

Summary

A case of ventricular tachycardia in a patient with an anterolateral ventricular aneurysm is reported. The aneurysm was excised and the ventricular tachycardia did not recur, despite discontinuation of quinidine.

Summario in Interlingua

Es reportate un caso de tachycardia ventricular in un patiente con aneurysma ventricular anterolateral. Le aneurysma esseva excidite. Le tachycardia ventricular non recurreva in despecto del discontinuation de quinidina.

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Congenital Coronary Arteriovenous Fistula Associated with Large Patent Ductus

By Lewis H. Bosher, Jr., M.D., Sverre Vasli, M.D., Carolyn Moore McCue, M.D., and Lester F. Belter, M.D.

SEVERAL excellent reviews have been published recently describing the anatomic and clinical findings in patients with congenital coronary arteriovenous fistulas or with communications between the coronary arteries and the cardiac chambers.[1-3]

The recognition of this clinical entity presents real difficulty, since it may easily be confused with other lesions causing a continuous or to-and-fro murmur, such as patent ductus arteriosus, aortopulmonary septal defect, ruptured aneurysm of an aortic sinus, interventricular septal defect with aortic insufficiency, and arteriovenous communications within the chest wall or lungs. In some instances only a systolic murmur has been recognized. For this reason both cardiac catheterization and angiocardiography are usually required for accurate diagnosis. Of the diagnostic measures available retrograde aortography affords the best opportunity for an accurate diagnosis.

We have collected 38 cases from the literature. The first case from Steinberg's paper was discarded, since the patient had an anomalous coronary artery arising from the pulmonary artery. Although functionally similar in some respects, cases with anomalous origin of coronary arteries are best placed in a separate category. The true figure may be higher, since, as Steinberg pointed out, some coronary artery aneurysms that were considered primary lesions may have resulted from arteriovenous fistulas that were not detected at autopsy.[3]

From the Division of Thoracic and Cardiovascular Surgery, Department of Surgery, and from the Departments of Pediatrics and Pathology, Medical College of Virginia, and the Congenital Heart Clinic of the Virginia State Health Department, Richmond, Va.

Analysis of the 39 cases including our own yields the following information.

In 19 cases the right coronary system was involved and the artery entered the coronary vein or sinus in 5,[4-8] the right atrium in 6,[2, 9-13] the right ventricle in 7,[8, 14-17] and the pulmonary artery in 1.[1]

In 16 cases the left coronary system was involved, and the artery entered the coronary vein or sinus in 4,[1, 18-20] the right atrium in 2,[21] the left atrium in 2,[22, 23] the right ventricle in 4,[24-27] the left ventricle in 2,[28, 29] and the pulmonary artery in 2.[30, 31]

In 1 case both right and left coronary artery systems participated in the communication with the pulmonary artery.[32] In 1 case both the right and left coronaries communicated through blood spaces in the myocardium with a common ventricle.[33] In 3 cases information regarding the exact anatomic arrangement was not available.[3, 34, 35]

It is apparent that left heart cavities are involved infrequently and indeed the term arteriovenous fistula appears inappropriate for these communications.

Associated congenital defects, which have been encountered in 6 cases, include pulmonary atresia, pulmonary atresia with interventricular septal defect, single ventricle, and patent ductus in 2. Indeed, in our case the patent ductus was by far the more important lesion, and the associated severe pulmonary hypertension seemed chiefly responsible for the death.

Our case, although completely studied preoperatively, remained undiagnosed. This is somewhat understandable in view of the associated large patent ductus that dominated the clinical picture and presumably caused severe pulmonary hypertension.

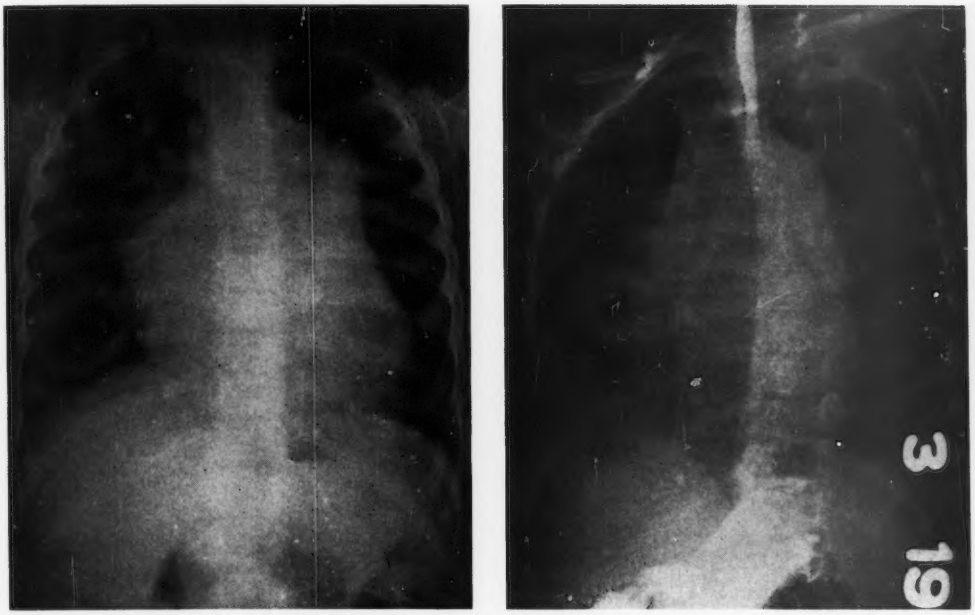


FIG. 1. Posteroanterior and left anterior oblique chest roentgenograms showing right atrial, right ventricular, and pulmonary artery enlargement.

CASE REPORT

R.C. This Negro female infant showed symptoms of cardiac failure at age 4 months. At 16 months she developed generalized edema and hepatomegaly and was digitalized. On March 19, 1956, at 18 months she was admitted to Dooley Hospital for study.

There was no evidence of cyanosis. The blood pressure was 88/48, the pulse was 120, the respirations were 80, and the weight was 16.5 pounds. The left hemithorax was prominent with a forceful apical heart beat. A thrill was noted over the left upper chest. A grade-IV systolic murmur was heard best in the third and fourth interspaces to the left of the sternum. The pulmonic second sound was considerably accentuated.

The chest roentgenograms showed considerable cardiac enlargement, particularly of the right ventricle (fig. 1). The pulmonary artery was greatly enlarged. The electrocardiogram showed right ventricular strain (fig. 2). The hematocrit value was 49 and the hemoglobin was 8.0 Gm. per cent.

Cardiac catheterization studies in March 1956 revealed a pulmonary artery pressure of 54/24 (table 1). There was an increase in oxygen saturation from the inferior vena cava to the right atrium of 20 per cent, from the low right ventricle to the high right ventricle of 13 per cent and from the low right ventricle to the pulmonary artery of 27 per cent. The tentative diagnoses were interatrial septal defect and patent ductus arteriosus. Interventricular septal defect and pulmonary insufficiency were also considered.

A retrograde brachial aortogram was advised but the family refused.

The child was readmitted to the hospital 1 year later on December 28, 1956. At that time the blood pressure was 90/60, the pulse was 140, respirations were 38, and the weight was 22 pounds. The physical findings were similar to those on the previous admission. The pulmonic second sound was perhaps more accentuated and there was a high-pitched, early diastolic murmur along the left sternal border suggesting pulmonary insufficiency. A note was made that no diastolic murmur could be heard to the right of the sternum and no mid-diastolic murmur at the apex of the heart. Occasional rales were audible at the lung bases. The liver was felt 2 cm. below the costal margin. The red cell count was 3.4 million, the hemoglobin 8.2 Gm. per cent, the blood urea nitrogen was 27 mg. The pulmonary artery, right ventricle, and possibly the right atrium were markedly enlarged on the roentgenograms. There was suggestive enlargement of the left ventricle. Increased pulsations were seen in the pulmonary vascular bed on fluoroscopy.

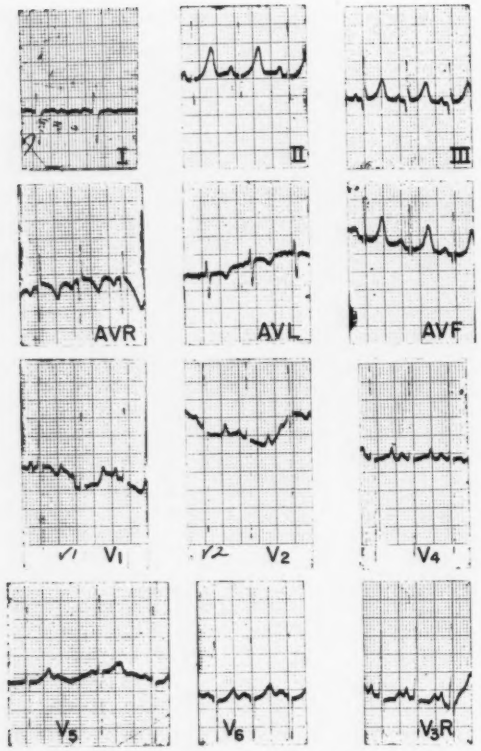


FIG. 2. Electrocardiogram showing right ventricular strain.

A retrograde aortogram was performed through the right brachial artery. The pulmonary artery and right heart both opacified at one half second and a patent ductus was thought to be visible. At one second there was definite opacification of the right atrium and hepatic veins. The pulmonary artery was obviously quite large (fig. 3).

On the basis of these findings a tentative diagnosis of large patent ductus arteriosus with pulmonary insufficiency and tricuspid insufficiency was made. The possibility of a ruptured sinus of Valsalva into the right ventricle was also considered, but the proper interpretation of the aortogram was not made.

The patient was admitted a third time for surgery on May 11, 1957. At the time of admission there was evidence of bronchopneumonia, and the temperature was 102 F. Crepitant rales were heard in the left lower lung field. There was a grade-III systolic murmur to the left of the sternum. The pulmonic second sound was loud and snapping. The liver was down 1 fingerbreadth. The hematocrit value was 44, and the hemoglobin was 12.3 Gm. per

TABLE 1.—*Cardiac Catheterization Data (March 1956)**

	Pressure	Per cent sat.	Hgb.
Main pulmonary artery		86.0	
Left pulmonary artery	54/20	84.0	
High right ventricle		70.0	
Low right ventricle	56/0	57.0	6.8
Low right atrium		57.0	
Inferior vena cava		37.0	
Femoral artery	80/24	97.8	
Left ventricular	output	5300 ml./min.	
Right ventricular	output	1800 ml./min.	
Patent ductus	shunt	3500 ml./min.	
Coronary to right atrium	shunt	600 ml./min.	

*Flows computed from oxygen consumption derived from Benedict's tables (for weight and age). Caval oxygen content based on inferior vena cava alone.

cent. An electrocardiogram again showed right ventricular strain. Chest roentgenogram showed evidence of congestion and patchy pneumonitis in the left lower lobe.

Operation was carried out through a bilateral transsternotomy incision 17 days later, after clearing of the pneumonitis. The pump oxygenator was prepared for possible use. A large patent ductus was found. Pressure readings were as follows: ductus opened, aortic pressure 76/40, mean 58, pulmonary artery pressure 76/40, mean 58; ductus closed, aortic pressure 84/50, mean 64, pulmonary artery pressure 58/28, mean 40. After division of the ductus there remained a thrill over the right atrium. Further examination revealed a vessel roughly 0.5 cm. in diameter, branching from a dilated left coronary artery and passing through the transverse sinus behind the aorta and pulmonary artery to empty into the right atrium behind the origin of the superior vena cava (figs. 4 and 5). The anomalous coronary vessel was ligated with several sutures near its entry into the atrium. No change occurred in the electrocardiogram.

For 24 hours after surgery the postoperative course was uneventful, but then the child died rather suddenly, apparently from a cardiac arrhythmia, about 30 hours postoperatively.

At postmortem examination there was intense pulmonary congestion of both lungs. The heart after fixation weighed 115 Gm., and there was hypertrophy of both ventricles. The left ventricle measured 7 mm., 7 mm., and 6 mm. at the base, midportion, and apex, respectively. The right ventricle showed an almost compact wall of hypertrophied

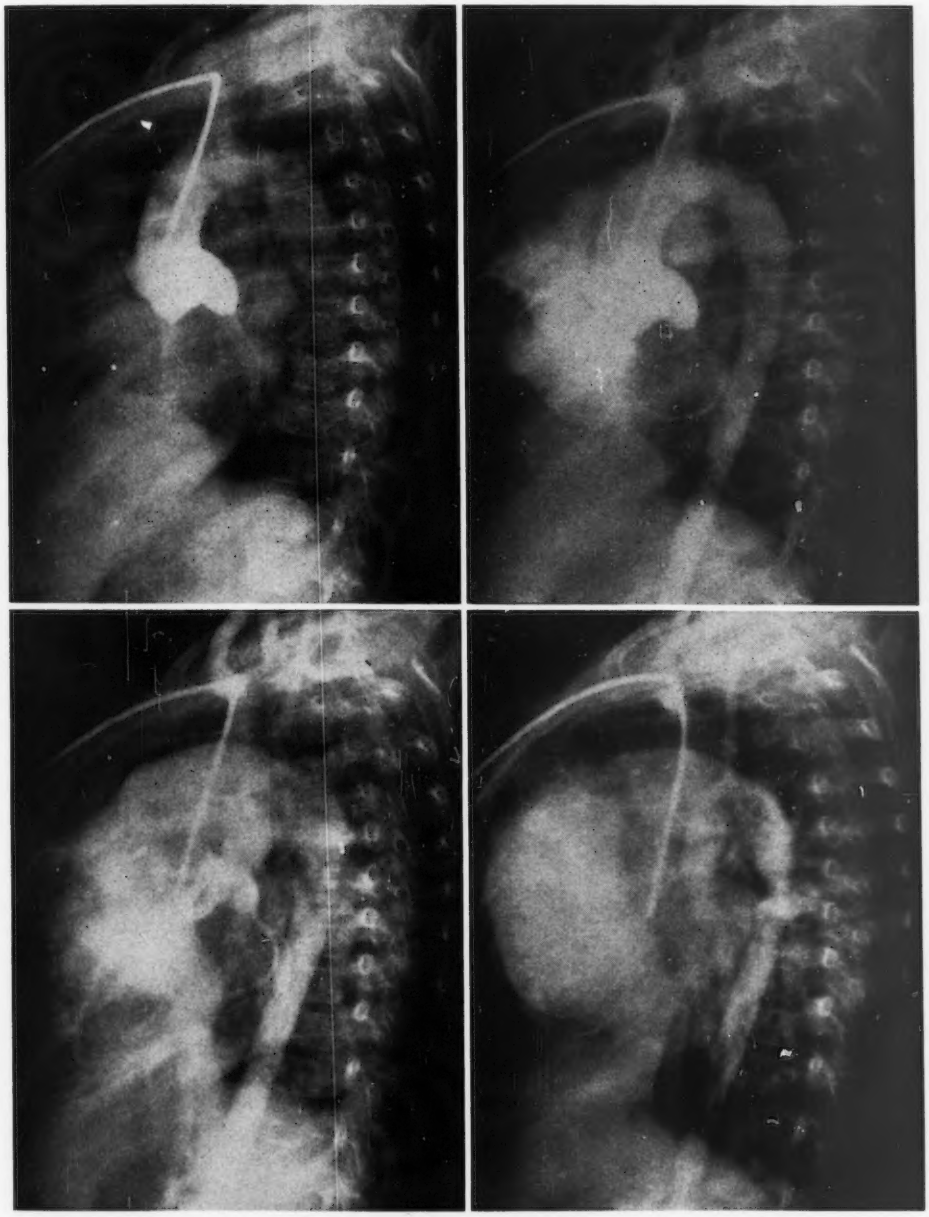
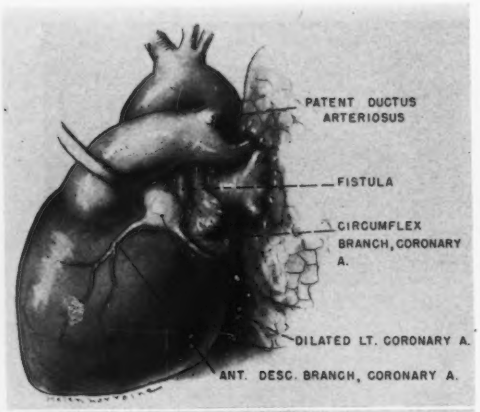


FIG. 3. Retrograde aortogram in extreme left anterior oblique position. *Top left.* Opacification of the aortic sinuses and aneurysmal dilatation of the first portion of the left coronary artery (0 sec.). *Top right.* Region of patent ductus seen. Pulmonary artery opacified. Right atrium well filled (0.5 sec.). *Bottom left.* Hepatic veins and right ventricle filling. Main pulmonary artery clearly outlined. Ascending aorta now empty. Aneurysmal dilatation of left coronary artery identified (1.0 sec.). *Bottom right.* Right ventricle well defined in diastole (1.5 sec.).



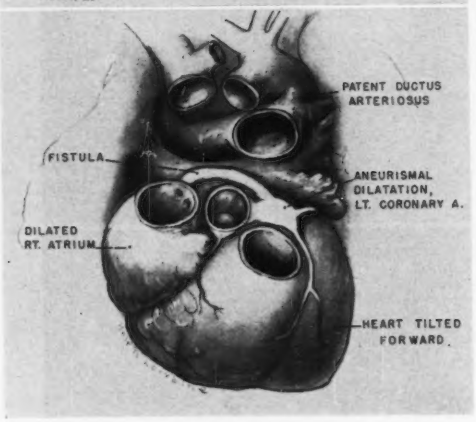


FIG. 4. Aneurysmal left coronary artery showing origin of anomalous branch as observed during surgery.

FIG. 5. Postmortem view showing course of anomalous coronary branch with entry into right atrium.

trabeculae carneae and measured 5 mm. at the base and 3 mm. at the apex, or 9 mm. and 6 mm. respectively when the trabeculae carneae were included. The orifice of the left coronary artery measured 8 mm. in diameter in the fresh state and opened into an aneurysmal dilatation of the vessel from which arose the anterior descending and circumflex branches and the anomalous coronary artery. The anomalous coronary artery coursed over the left atrial wall through the transverse sinus and entered the right atrium by a 2 mm. orifice. The anomalous channel was almost cylindrical, being reduced only at the distal opening. The measurements of the circumference of the coronary arteries in the fixed state were right 4 mm., left descending 4.5 mm., left circumflex 4 mm., and anomalous 11 mm.

Histologic examination of the shunt revealed a greatly thickened wall containing little muscle tissue in some portions of the wall and a great excess of elastic tissue and collagen (fig. 6). The amount of connective tissue varied throughout the wall and produced irregularly thickened areas. Histologic examination of the pulmonary vessels revealed only minimal change despite the high pulmonary arterial pressure.

DISCUSSION

If a congenital coronary arteriovenous fistula had been suspected, the diagnosis could probably have been made from the evidence on the retrograde aortogram. In retrospect the aneurysmal dilatation of the left coronary is well opacified at .5, 1, and 1.5 seconds, and the various branches are clearly seen at 1 second. The opacification of the right atrium was heavy, and even the hepatic veins filled. Since the aortogram also demonstrated a patent ductus we explained the opacification of the right heart as due to pulmonary insufficiency, which was present clinically, and tricuspid insufficiency. However, such an explanation seems illogical in retrospect, in view of the strong opacification of the right atrium. The possibility of a ruptured aneurysm of the sinus of Valsalva into the right atrium was entertained and in fact was the chief reason for preparing the pump oxygenator. However, this interpretation of the aortogram involved the assumption of an aneurysm of the *left* coronary sinus, a very rare condition. Rupture into the right atrium would not be anticipated.[36, 37]

In most cases the murmur has been described as continuous, sometimes closer to the ear than one usually associates with a patent ductus. However, to-and-fro murmurs and systolic murmurs have been described. In our case the loud systolic murmur of the patent ductus possibly obscured any murmur that might have originated from the arteriovenous fistula.

The electrocardiographic findings are available in 17 cases and were normal in 8. In others either coronary artery disease or unrelated cardiac defects were present and could well explain the electrocardiographic changes

Right axis deviation and atrial fibrillation were found in 1 patient with congestive heart failure in whom a large shunt passed from the left coronary artery to the coronary sinus. S-T and T-wave abnormalities occurred in a patient in whom the right coronary communicated with the pulmonary artery. In the patient discussed by Edwards and Burchell[37] electrocardiographic evidence of ischemia was thought to be due to the coronary arteriovenous fistula between the right coronary and and right atrium. In our own case right ventricular strain can be attributed to the presence of patent ductus arteriosus and pulmonary hypertension.

Of interest is the size of the arteriovenous communication, which in the majority of reports has ranged from 1 to 3 mm. Somewhat larger fistulas ranging in diameter from 5 to 20 mm. were described by Trevor,[15] Mozen,[22] Baylis and Campbell,[30] and Fell et al.[14] In our own case the opening was found to be approximately 2 mm. Nevertheless a moderate-size shunt was present, as evidenced by aortography and by the calculation from cardiac catheterization data. From the small amount of data available it is apparent that shunts of considerable magnitude have been encountered: 2.0,[1] 1.7,[26] 5.2,[1] 3.9,[16] 0.59 L. (this paper), or expressed as per cent of left ventricular output: 29, 39, 47, 55, and 11.

We have examined all of the reported cases to determine in what number abnormally positioned coronary arteries contributed to the fistula. Brown and Burnett[26] reported an accessory left coronary that arose from the aorta and entered the right ventricle at the lower border of the pulmonary conus. Björk and Crafoord[31] described an abnormal artery, arising as a branch of the left coronary, which crossed the pulmonary artery and communicated with this vessel. In the case presented by Johnson[13] an anomalous right coronary coursed behind the aorta and superior vena cava to enter the right atrium. In our case an anomalous branch of the left coronary artery took a similar course behind the aorta and pulmonary artery and entered the right atrium behind the superior vena cava at its junction with this chamber.

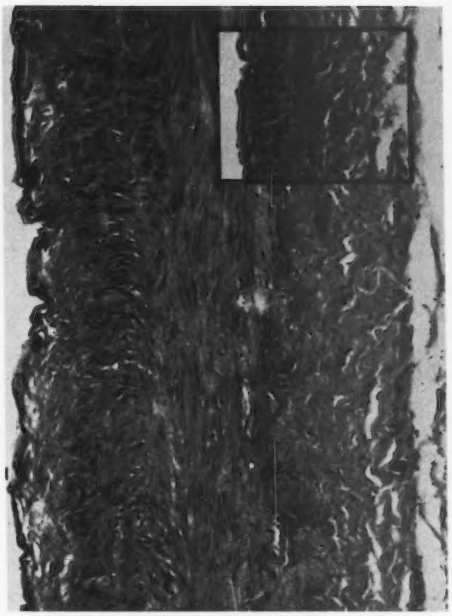


FIG. 6. Abnormal coronary artery, full thickness × 100, compared with insert of left circumflex artery, × 100, showing great increase of collagen in abnormal vessel.

The physiologic importance of the lesion and the prognosis for these patients must vary with the volume of the arteriovenous shunt. Although a number of the patients have remained asymptomatic, others have shown significant degrees of cardiac enlargement and even congestive heart failure. Other complications include subacute bacterial endarteritis and myocardial ischemia developing in the area beyond the arteriovenous communication.[2] Associated aneurysms have been present in some of the cases and in 5 of these thrombus formation was found in the aneurysm.[2, 11, 12, 31, 32] Complete clotting of the anomalous vessel and aneurysm occurred in 1 of these.[31] Dilatation, sometimes of aneurysmal proportion, may be expected in the proximal coronary artery.[12, 14, 15, 32, 33]

In view of the numerous possibilities for complications, surgical treatment should usu-

ally be recommended. Of the 39 cases 17 have been submitted to surgery.[1, 7, 8, 11–14, 22–24, 27, 31, 35] In 4 of these exploration only was performed. Ligation of the involved artery or arteries has appeared to be a curative procedure and was accomplished in all of the other cases. An aneurysm at the site of the communication may require excision or incision to allow closure of the fistulous communication with the cardiac chamber. In the occasional case the problem may appear so formidable that the surgeon may find it useful to employ extracorporeal circulation with cardiac arrest.[14] Of the 13 cases in which definitive surgery was attempted all survived except the 1 reported in this paper.

Summary

An unusual case of congenital coronary arteriovenous fistula is reported, bringing the total number of reported cases to 39.

This is the second case in which the left coronary artery system communicated directly with the right atrium, and also the second case associated with a patent ductus.

Our case is well documented by cardiac catheterization data, retrograde aortography, and postmortem findings.

Although surgical correction of both the patent ductus and coronary arteriovenous fistula was accomplished without great difficulty, the patient died 30 hours postoperatively, presumably from the effects of severe pulmonary hypertension.

Summario in Interlingua

Es reportate un caso inusual de congenite fistula arterio-venose coronari. Illo augmenta le numeral de tal casos reportate in le litteratura a un total de 39.

Isto es le secunde caso in que le systema del arteria coronari sinistre communica directemente con le atrio dextere. Illo es etiam le secunde caso associate con ducto patente.

Nostre caso es ben documentate per catheterisation cardiac, aortographia retrograde, e datos necropsial.

Ben que le correction chirurgic del ducto patente e del fistula arterio-venose coronari esseva effectuate sin grande difficultates, le patiende moriva 30 horas post le operation apparentemente como resultato de sever grado de hypertension pulmonar.

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Reversible Wenckebach Type Atrioventricular Block Associated with Severe Coronary Artery Disease

By Hershel Jick, M.D., and Arthur J. Linenthal, M.D.

HIGH-grade atrioventricular heart block in patients with coronary artery disease is generally thought to be irreversible and in most cases atropine produces little or no effect.[1] Nevertheless, the possibility of significant vagal action should always be considered in any patient with heart block. When such a factor is present, the administration of atropine will produce a striking improvement in atrioventricular conduction.

We are presenting detailed observations on an unusual patient with heart block: chronic atrioventricular block of the Wenckebach type was associated with severe coronary artery disease and congestive heart failure; atropine abolished the block, prevented Stokes-Adams attacks, and controlled an increase in the block that was produced by digitalis. These observations indicate that there may be functional as well as organic components in this type of heart block, and emphasize the importance of testing the effects of atropine in such patients.

Case History

L. R., an 85-year-old man, was admitted to the Beth Israel Hospital in October 1955 because of increasing congestive heart failure. He had had 2 acute myocardial infarctions (in 1943 and 1951) followed by angina pectoris and congestive heart failure. In 1951 he began to have episodes of syncope associated with first-degree heart block (P-R interval 0.30 second) and sinus bradycardia (rate 55 to 60 per minute). Frequent episodes of lightheadedness and occasional attacks of syncope occurred during the ensuing 4 years. Partial heart block with the Wenckebach phenomenon was present for at least 3 years prior to 1955.

Repeated attempts at digitalization, both at home and in the hospital under close observation, had been unsuccessful because drug administration was associated with increased heart block. Frequent periods of 2:1 atrioventricular block were produced with ventricular rates as low as 30 beats per minute.

On examination severe congestive heart failure was found. An electrocardiogram (fig. 1*A*), as in the past, showed sinoatrial bradycardia and atrioventricular block with Wenckebach periods.

During this admission it was decided to analyze in detail the patient's conduction defect in an attempt to clarify both the response to digitalis and the mechanism of the syncopal episodes. The effects on conduction of atropine, carotid sinus pressure, digoxin, and exercise were studied. Atropine abolished the spontaneous block and produced normal atrioventricular conduction. Carotid sinus pressure, digoxin, and exercise increased the conduction defect; in each case atropine prevented the increase. These observations form the basis of this report and are detailed in the next section.

Observations

The cardiac effects of carotid sinus pressure, atropine, digoxin, and exercise were studied over a 27-day period; 124 electrocardiograms were taken on 17 days during this period. Each electrocardiogram was recorded from lead I for at least 1 minute; most tracings were longer, some as long as 4 minutes when dropped beats were infrequent or absent. All electrocardiograms unless otherwise specified were taken with the patient at rest in bed in a semirecumbent position for at least 10 minutes.

The following measurements were obtained from each electrocardiogram: (1) the maximum and minimum P-P intervals during a period of at least 1 minute; (2) the sinoatrial rate (beats per minute) determined by counting the number of P waves in 15 to 60 seconds; (3) the maximum and minimum P-R intervals during a period of at least 1 minute; (4) the average number of dropped beats (nonconducted P waves) per minute determined from the full length of each tracing; (5) the ventricular rate (beats per minute) determined

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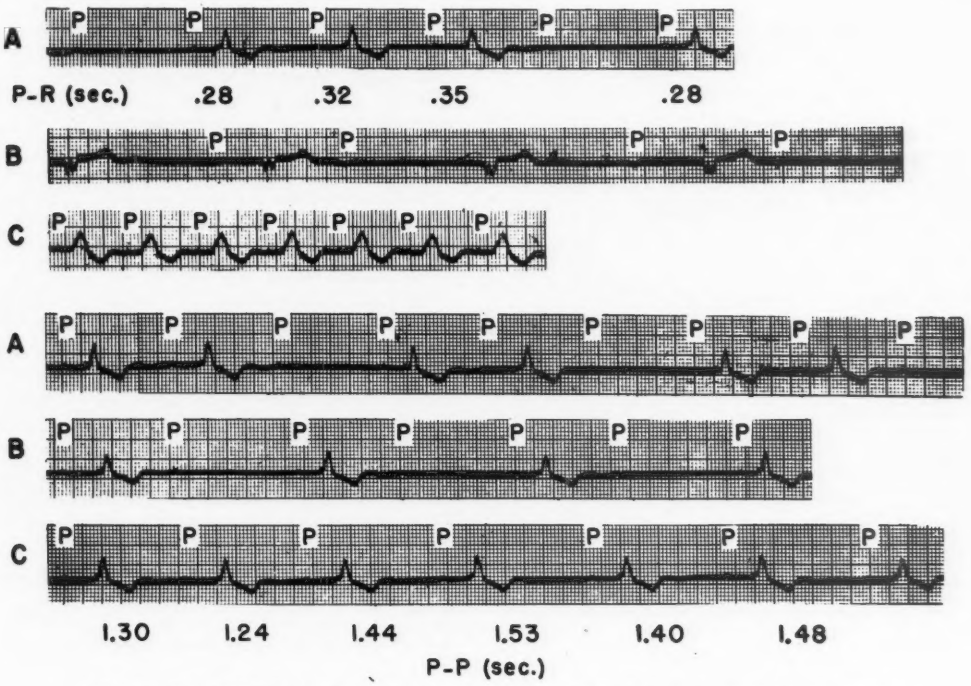


FIG. 1 *Top.* Lead I. *A.* Control: sinoatrial bradycardia (P-P 1.24 seconds) and partial atrioventricular block. There is progressive increase in the P-R intervals before the nonconducted P wave (Wenckebach-type block). *B.* During right carotid sinus pressure: complete atrioventricular block (P-P 1.40 seconds, R-R 2.0 to 2.2 seconds). *C.* Three minutes after intravenous atropine: sinoatrial rhythm (P-P 0.72 second) with normal atrioventricular conduction (P-R 0.16 second).

FIG. 2 *Bottom.* Lead I. Digoxin effects: *A,* 3:2 atrioventricular block; *B,* 2:1 atrioventricular block (R-R 2.28 seconds); *C,* sinoatrial arrhythmia.

by subtracting the number of dropped beats from the sinoatrial rate.

Effects of Carotid Sinus Stimulation

Light pressure applied to either the right or the left carotid sinus (day 7) produced complete heart block with a slow indioventricular rhythm (fig. 1*B*); there was no change in the sinoatrial rate.

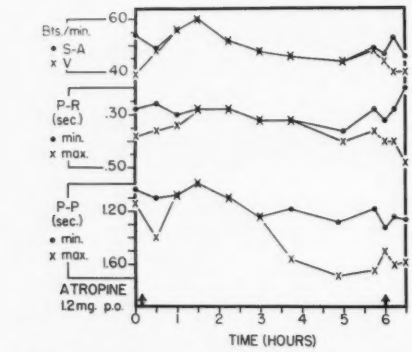
Effects of Atropine

One milligram of atropine sulfate intravenously (day 11) completely abolished the spontaneous atrioventricular block; the P-R interval became normal (0.16 second) and dropped beats disappeared, despite a marked increase in the sinoatrial rate (fig. 1*C*). At the time of this atropine effect firm pressure applied to either carotid sinus had no effect on atrioventricular conduction or on the sinoatrial rate.

Atropine sulfate administered subsequently by mouth also improved atrioventricular conduction: 2 hours after 0.6 mg. (day 12) dropped beats were absent and the P-R interval was stable at 0.28 second; 3½ hours after 1.2 mg. (day 13) dropped beats were absent and the P-R interval was stable at 0.22 second. Atropine in doses of 1.2 mg. by mouth every 6 hours produced moderate dryness of the mouth.

Combined Effects of Atropine and Digoxin

Atropine sulfate and digoxin were administered simultaneously for 6 days (days 13 to 18): 1.2 mg. of atropine sulfate by mouth every 6 hours and a total of 2.0 mg. of digoxin (0.75 mg. intramuscularly on day 13 and then 0.25 mg. by mouth daily for 4 days). During the first 5 days the P-R interval (determined 4 hours after a dose of atropine) gradually increased: on the fourth day of combined drug therapy (day 16) it was 0.26 second; on the fifth day (day 17) 0.32 second. On the sixth day (day 18) there were periods of 3:2 block, 2:1 block, and marked respiratory sinus arrhythmia (fig. 2). With this high degree of block



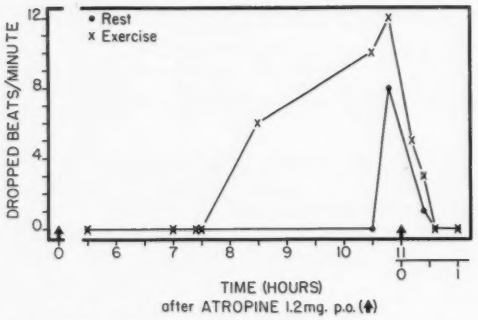


FIG. 3 *Top.* Combined effects of atropine and digoxin on sinoatrial rate and rhythm and on atrioventricular conduction.

FIG. 4 *Bottom.* The effects of exercise on the atrio ventricular conduction defect.

the ventricular rate was sometimes as low as 4 beats in 10 seconds and the patient complained of lightheadedness and dizziness. Accordingly, digoxin was omitted and atropine administration (1.2 mg. by mouth every 6 hours) was continued.

The action of atropine sulfate was studied in detail (days 19 to 23) as the effects of digoxin on atrioventricular conduction disappeared. Figure 3 shows the changes observed between 2 oral 1.2 mg. doses of atropine sulfate given 6 hours apart on the second day after the digoxin was stopped (day 20). At the time of the first dose, there were 16 dropped beats per minute, the P-R interval varied between 0.28 and 0.38 second, and the P-P interval ranged from 1.05 to 1.13 seconds. At the height of the atropine effect, 1½ hours after the dose, all sinoatrial beats were conducted to the ventricle, the P-R interval was stable although still longer than normal, and there was no sinus arrythmia. At 3½ hours after the dose, the sinus arrhythmia reappeared, at 5 hours the P-R interval again began to vary, and at 5½ hours dropped beats were again observed.

On the following day (day 21) also, dropped beats reappeared 5½ hours after a dose of atropine sulfate. However, on the fourth and fifth days after the omission of digoxin (days 22 and 23) no dropped beats were noted at any time, just as had been the case before digoxin was started (days 12 and 13). The P-R interval varied from 0.24 second (1 to 3 hours after a dose of atropine sulfate) to 0.28 second (5 to 6 hours after a dose of atropine sulfate).

Effects of Exercise

All these observations were carried out with the patient at rest, since it was frequently noted that exercise increased the number of dropped beats. This effect of exercise was studied by taking electrocardiograms after the patient had performed 3 consecutive sit-ups in bed from a semirecumbent position.

On days 20 and 21, when a definite digoxin effect was present, 5 observations on the effect of exercise were made 5 to 6 hours after a dose of atropine at a time when dropped beats were occurring at rest: in each case exercise increased the number of dropped beats per minute (by 3 to 10). On day 22, when there was no longer a digoxin effect and atropine completely prevented dropped beats at rest, exercise had no effect when tested 5 times between 3½ and 6 hours after a dose of atropine.

In order to study the effects of exercise in the absence of digoxin or atropine effects, a single dose of atropine was omitted on day 23 and the effects of exercise were observed for 11 hours after the last dose (fig. 4). Dropped beats appeared with exercise 8½ hours after the dose; they did not appear at rest until 2¼ hours later. When dropped beats were present at rest, exercise increased their frequency, so that there were occasional periods of 2:1 block. With the mild exercise that was sufficient to increase the conduction defect no change was observed in the resting sinoatrial rate, which varied between 56 and 62 beats per minute.

A new, long-acting preparation of atropine (Prydon) was tested on day 28: 0.8 mg. by mouth prevented dropped beats for at least 12 hours both at rest and with exercise. At the time of discharge on the thirty-second hospital day the patient was receiving 0.8 mg. of this preparation by mouth twice a day and he was free of Stokes-Adams attacks.

DISCUSSION

This patient with heart block of the Wenckebach type had a remarkable lability of atrioventricular conduction, which served as an extremely sensitive indicator of extracardiac influences on the conduction mechanism.

Atropine abolished the spontaneous block, indicating that the conduction defect was caused by intrinsic vagal activity. This observation is striking, since it is most unusual for atropine to abolish such a high degree of heart block in a patient with severe coronary artery disease.[1]

Carotid sinus pressure, digoxin, and exercise increased the block. These effects were of vagal origin as shown by the fact that atropine abolished them.

Marked sensitivity of the heart to reflex vagal stimulation is often observed in patients with coronary artery disease as shown by the frequent finding of a hyperactive carotid sinus reflex.[2] Usually the sinoatrial node is more sensitive to carotid sinus stimulation than the atrioventricular node, and considerable slowing of the sinoatrial rate occurs before there is any appreciable effect on conduction.[3] In this patient, however, the atrioventricular node was far more sensitive than the sinoatrial node, and light carotid sinus pressure produced complete heart block although there was no slowing of the sinoatrial rate.

That digoxin increased the block in this patient is clear on the following grounds: the same phenomenon had been observed several times before when a cardiac glycoside had been given; such high degrees of block (3:2 and 2:1) were never observed in the resting state at other times; and conduction returned to its previous state 4 days after digoxin was stopped, as would be expected from the known duration of action of the drug. Although cardiac glycosides do not ordinarily affect preexisting heart block,[4] it is well recognized that they may interfere with atrioventricular conduction through a vagal mechanism as was observed in this patient. This vagomimetic action should not be confused with the direct action of the glycosides on conduction, which may be observed with larger doses and which is not changed by atropine. The sinus arrhythmia associated with digoxin was also a vagal effect; this respiratory arrhythmia increases as vagal action on the sinoatrial node increases.

The vagomimetic effect of exercise observed in this patient is contrary to what we might have expected, since exercise is generally associated with sympathetic stimulation and vagal inhibition. Indeed, others have observed in individuals without heart disease that Wenckebach block reversible by atropine is also abolished by exercise.[5, 6] The effect of exercise in this patient with severe coronary artery disease, however, may have been associated with slight alterations in coronary blood flow or may be explained by accepted neurophysiologic phenomena. Cessation of reflex stimulation of the sympathetic pathways may be followed by rebound overactivity of the previously inhibited vagal pathways.[7] Thus, immediately following exercise in this patient, when the vagomimetic effect was observed, there may well have been a rebound of the previously inhibited vagal supply to the atrioventricular node. It should be emphasized that the effect of exercise was observed only at the atrioventricular node; there was no associated increase in the sinoatrial rate, which might otherwise have explained the increased block.

The observations in this patient are all consistent with localized changes in the atrioventricular node, causing an increase in its sensitivity to neurogenic and pharmacologic stimuli. Similar localized sensitivity has been described in another patient with coronary artery disease and a hyperactive carotid sinus cardiac reflex, and may be attributed to degenerative changes in the intrinsic cardiac ganglia or in the nodal tissue.[8]

These observations were valuable in the clinical management of this patient by clarifying his response to digoxin. Digitalization was impractical because uncomfortable dryness of the mouth occurred, even with doses of atropine that only partially controlled the increased block. However, in an emergency, it was thought that digitalization could be safely accomplished by simultaneously giving larger doses of atropine.

This patient with partial atrioventricular block had Stokes-Adams disease manifested by attacks of syncope or other symptoms of cerebral ischemia due to a slow ventricular rate. Complete heart block was observed with carotid sinus pressure (fig. 1*B*) and periods of 2:1 block with either exercise or digoxin administration; in either case ventricular rates were slow enough to produce cerebral ischemia. Atropine in doses that did not produce dryness of the mouth prevented these attacks. This therapeutic effect of atropine in our patient is unusual, since in most cases of Stokes-Adams disease the heart block is not affected by the drug.[9]

Summary

A patient with severe angina pectoris and congestive heart failure had chronic Wenckebach-type atrioventricular block and episodes of syncope. Atropine abolished the block and prevented the Stokes-Adams attacks. Carotid sinus pressure, digoxin, and exercise increased the block; atropine prevented these effects.

Summario in Interlingua

Un patiente con sever angina de pectore e congestive disfallimento cardiac habeva chronic bloco atrio-ventricular del typo Wenckebach e episodios de syncope. Atropina aboliva le bloco e preveniva le attaccos de Stokes-Adams. Pression al sinus carotidic, digoxina, e exercitio augmentava le bloco. Atropina preveniva iste effectos.

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Aortic stenosis was clinically diagnosed in 326 patients from the Johns Hopkins Hospital and the Cardiac Clinic of the Harriet Lane Home. Sixty-three of the 326 patients were found to have neurologic manifestations such as syncope, headaches, convulsions, dizziness, hemiparesis, and deafness. Hemiparesis occurred in 7 patients with acquired aortic stenosis, but did not occur in any of the patients with congenital aortic stenosis; deafness occurred in 3 patients with the congenital lesion, but in none of the patients with acquired aortic stenosis. Syncope and seizures were the most common neurologic manifestations occurring in 36 of the 63 patients.

Karpman

Takayasu's Disease

A Case Report with an Angiocardiographic Study

By JOHN COSMA, MAJOR, M.C., YOSH MARUYAMA, CAPTAIN, M.C.,
J. R. PETTET, MAJOR, M.C., AND VINCENT CUTSHALL, CAPTAIN, M.C.

WE HAVE recently had the opportunity to study a young Japanese woman with so-called "Takayasu's" or "pulseless" disease. Although angiocardiographic studies have been done previously,[1, 2] we believe this case to be the first in which such clear-cut confirmation of the gross pathology of this condition has been demonstrated by this method.

REVIEW

The original case report by Takayasu in 1908[3] in the medical literature of Japan noted only the eye findings, and later authors[4-7] described the condition more completely. The condition is known by any number of terms, of which the most popular is pulseless disease. Takayasu's disease represents a prototype of the so-called "aortic arch syndromes," a term first used by Ross and McKusick. This latter term implies a number of different causative factors, and of the cases in the occidental medical literature, most are due either to syphilis, with its aortitis and aortic aneurysms, or to arteriosclerosis. In Japan, however, it is usually due to a peculiar form of panarteritis of the great vessels which has been studied most extensively by the Japanese. It appears to be a distinct entity, of yet unknown etiology, occurring largely in young females. Of the 122 cases reported in Japan, 111 were females and 11 were males. Sano and Shimizu, of Tokyo University, noted only 2 men in 36 hospitalized patients. This type of panarteritis has only rarely been noted in the rest of the world, but in view of some reports it does unquestionably occur.[1, 2, 4, 5, 9-30] Other causes of "aortic arch syndrome" include chronic dissecting aneurysms, congenital abnormalities, upper mediastinal tumors, trauma, thrombophilia, and neurogenic and thoracic outlet syndromes. The etiology of idiopathic panarteritis of the great vessels in unknown. It may possibly fall into the spectrum of "collagen diseases."

The clinical features of this interesting disease are the consequence of obstructed blood flow to the cerebral, visual, and vascular systems. The most striking changes are of the vascular system and are noted in the peripheral pulses. These findings are noted in the main branches of the aortic arch; namely, the subclavian and carotid arteries and in their more peripheral branches. Though early in the disease there may be simply asymmetry of the pulse, there is eventual progression to a complete obliteration. Additional findings include thrills and bruits over the involved vessels prior to complete occlusion, differences or inability to measure

FIG. 1. Left carotid arteriogram. The dilatation and stenosis are well demonstrated. (Performed at Tokyo Women's Medical College. Film obtained through the courtesy of Drs. Shimazu and Nakayama.)

From the Tokyo Army Hospital, Tokyo, Japan.

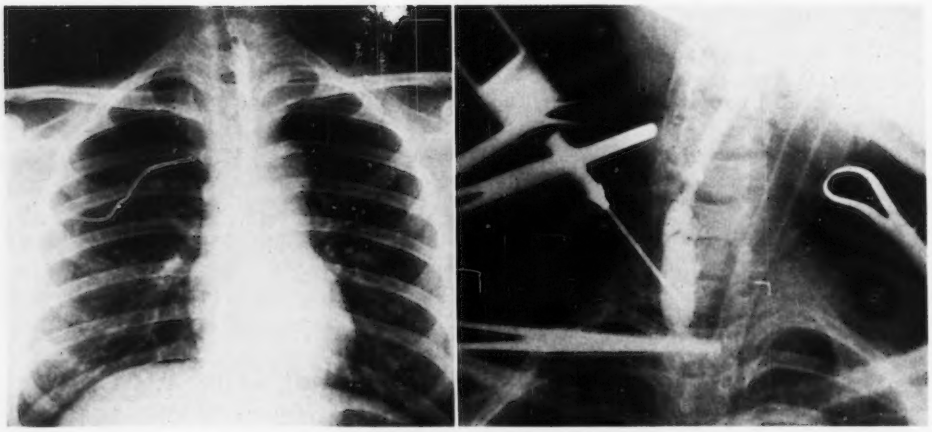

FIG. 2 *Left.* Posteroanterior chest film with barium swallow. Note widening of the upper mediastinum, prominence of the aortic knob, and tortuosity of the aorta. The aortic outline can be seen through the cardiac silhouette.

FIG. 3 *Right.* Right carotid arteriogram. The aneurysm of the base of the common carotid is evident with stenosis proximally. Stenosis of the midcarotid region, probably due to irregular thrombus formation, is also demonstrated. The distal vessel appears normal.

the blood pressures in the arms, collateral thoracic circulation, and marked hypersensitivity of the carotid sinus in the more advanced stages of the disease. Hypertension of the lower extremities has been noted in some cases. Though trophic changes of the head and neck and sometimes perforated nasal septi occur, ischemic ulcers of the upper extremities have not been seen. Symptoms include cervical pain and tenderness over the vessels, fatigability, and claudication of the arms, shoulders, and jaws. Pain, coldness, weakness, and paresthesias of the arms, shoulders, and back have been noted.

The visual signs and symptoms develop with gradually diminished blood flow. The symptoms are flashes of light, field defects, altered visual acuity, visual disturbances on changing position, and eventually in the late stages, blindness. The findings in the retina are pallor and new vessel formation, especially around the optic papilla. Cataracts develop in the late stages. Optic atrophy, retinal atrophy and pigmentation, atrophy of the iris, microaneurysms, sluggish blood flow, decreased ocular pressure, enophthalmos, and superficial keratitis have been seen.

The cerebral symptoms are among the most important. They include aches, dizziness, syncope, vertigo, epileptiform seizures, transitory hemiplegias and hemiparesis, aphasia, mental and memory impairment, and emotional lability. They can be most troublesome on positional changes that reduce the cerebral blood flow. These may be due to an abnormally sensitive carotid sinus. Eventually death results from cerebral vascular insufficiency.

The single almost consistent laboratory finding is an elevated sedimentation rate. The Wassermann test is usually negative. In Japan a high percentage of tuberculin reactors[7] has been noted but it is difficult to evaluate in view of the high incidence of tuberculosis in the population. Other laboratory studies except for the oscillometric studies show no consistent pattern.

As to prognosis, the course is quite variable and remitting and may be quite long. A number of cases have been followed for periods over 10 years.[31] Ash-Upmark[8] and Jervell[21] have observed cases to 14 years.

Pathologically, involvement of the aorta and of the vessels leading from the aortic

arch have been repeatedly demonstrated.[9, 14, 19, 22, 26, 28, 29, 32] All or part of the thoracic and abdominal aorta may be involved, though affinity for the more proximal portions has been noted. The pulmonary artery has also been involved. The walls of the vessels are thickened, and extensive perivascular adhesions between the adventitia and surrounding tissues have been seen. The chronic inflammatory process involves the adventitia, media, and endothelium, and thrombus formation occurs with partial or complete obliteration of the lumens of supra-aortic and other branches of the aorta. Recanalization has also been seen. Round-cell infiltration involves all the layers of the vessel wall, and giant cells have also been noted in the inflammatory reaction. The more peripheral branch vessels are unremarkable until the disease is quite far advanced.

Case Report

One year prior to entry, the patient, I.P., a 19-year-old Japanese bride of an American serviceman, had noted severe generalized headaches associated with marked pain and tenderness of the left anterior cervical region. This had cleared spontaneously after several months, and no further symptoms were noted until September 1957. At that time, there was a recurrence of pain in the left side of the neck, and the patient was seen at the Tokyo Women's Medical College. The presence of an aneurysm of the left carotid artery was noted in an area of tenderness in the midneck region. A left carotid arteriogram (fig. 1) showed an aneurysm. The symptoms then partially cleared, but again recurred in late October, this time involving the right side of the neck. On November 2, 1957, the patient complained of severe right-sided headaches, nausea, and vomiting of 1 week's duration. An aneurysm of the base of the right common carotid artery just above the sternoclavicular joint and signs of partial obstruction were noted. The patient was admitted to the Tokyo Army Hospital.

There had been minor trauma to the right side of the neck in the early teens with no difficulty until the present illness. Some shoulder and back aching was noted occasionally. She was unaware of any change in her peripheral pulses, and noted no visual or cerebral symptoms other than occasional headache. These latter symptoms were adequately controlled with aspirin.

The past and family histories were noncontributory. She denied tuberculosis or syphilis.

Fig. 4. Early phase angiocardiogram. The pulmonary arteries and vessels appear unremarkable.

Menarche was at 14 years and periods were regular at monthly intervals.

The patient was well developed and nourished. Significant physical findings were confined to the cardiovascular system. The left radial pulse was weakly palpable, the right was normal. The blood pressure on the right and left was 120/80 and 100/80, respectively. In the neck both carotid pulses were full, although the pulsations on the left were slightly less. There was an expansile aneurysm of the base of the right common carotid artery just above the sternoclavicular joint. A thrill was easily palpable, and a loud systolic bruit was noted over the region and distally. The vessel wall appeared to be indurated. In the left carotid region similar findings were noted. The aneurysm was in the midcarotid region. The left subclavian pulse was weakly palpable and the right was full. The abdominal aorta was unremarkable, and both femoral and pedal pulses were full and symmetrical. The blood pressures in the legs were both 140/90. Both fundi were negative. The heart was not enlarged and the rhythm was regular at a rate of 84. No murmurs were noted.

Cardiolipid determinations were normal. A tuberculin test was negative. The corrected sedimentation rate was 36 and 42 mm. per hour, and the C-reactive protein was elevated at 5½ units. Total protein was 7.5 Gm. per cent, albumin 3.2 Gm. and globulin 4.3 Gm. per cent. Serum cholesterol was 297 and 286 mg. per cent on 2 occasions and the esters were 195 and 167 mg. per cent respectively. Multiple other studies were negative, including hemoglobin, hematocrit level,

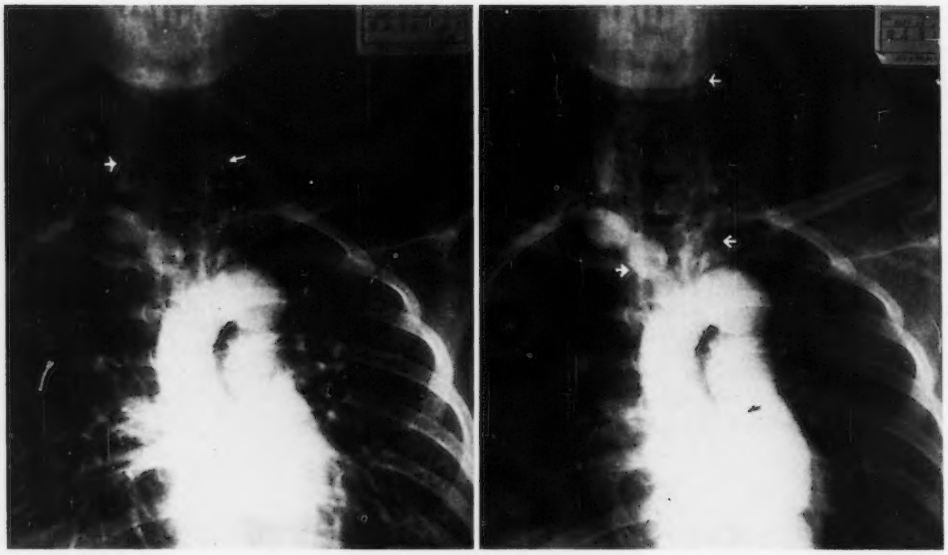

FIG. 5 *Left.* Angiocardiogram. The irregular dilatation and stenosis of the proximal aorta are well seen. This early film shows the prompt appearance of the contrast media in the vertebral arteries (*arrow*).

FIG. 6 *Right.* Angiocardiogram. Demonstrates the double innominate pattern (*arrow*) of the great vessels as well as areas of stenosis and dilatation in these vessels and the aorta. The right common carotid artery is also seen and reveals the same changes noted on the previous arteriogram. The left common carotid artery is poorly seen. An aneurysm of this vessel can be seen in the mid-neck region (*arrow*). The extensive involvement of the entire aorta in the thoracic region is demonstrated. Note the left brachial artery which appears unremarkable.

white blood count, reticulocyte and platelet counts, bleeding and clotting times, clot retraction, prothrombin time, blood urea nitrogen and glucose, urinalysis, cephalin flocculation and thymol turbidity tests, van den Bergh test, alkaline phosphatase, serum glutamic acid transaminase level, cell preparations for lupus erythematosus disseminatus, and electrocardiogram.

Roentgen studies showed clear lung fields (fig. 2). The heart was not enlarged; however, the upper mediastinum was widened. The aortic knob was markedly prominent and the aorta was slightly elongated. Fluoroscopy confirmed the widening and no pulsations were seen in this region. The aorta was knobby and the amplitude of the pulsations was noted to be damped. Laminography confirmed the widening of the upper mediastinum but no further information was obtained.

In view of the possibility of an arteriovenous fistula, it was decided to explore the right side of the neck. On November 12, operation disclosed evidence of arteritis and periarteritis. The common carotid artery was leathery, thickened, and indurated with an aneurysm at its base and stenosis in the midcarotid region from intravascular thrombus formation. A marked thrill, palpable over the stenotic area, disappeared on opening the carotid sheath. An aortogram was attempted but was unsuccessful. In view of the marked inflammatory changes, no biopsy was done. A right carotid arteriogram (fig. 3) confirmed the presence of an aneurysm of the right carotid artery with stenosis both at the proximal region of the aneurysm and distally. The distal portion was shaggy and irregular, suggestive of intravascular thrombus formation. Angiocardiographic studies on November 22, 1957 (figs. 4-6), showed evidence of diffuse involvement of the aorta and its main brachiocephalic branches. The pulmonary arteries were unremarkable. The entire thoracic aorta exhibited alternating stenotic and dilated regions. Its main branches were of the double innominate pattern,[33] and the left common carotid artery was poorly seen. The major cerebral flow appeared to be through the vertebral arteries. These vessels also showed irregularities in contour.

Following discharge the patient again noted minimal pain and tenderness of the left carotid region. On a follow-up visit 1 month later she described back and shoulder pains but was otherwise unchanged. She came to the United States with her husband in January 1958.

Discussion

The symptoms and findings of this type of "idiopathic panarteritis of the great vessels" are reviewed and a case of this condition in its early clinical stages is reported. The most interesting feature of this case is the angiocardiographic study and its correlation with the previously observed pathologic findings. The extensive involvement of the aorta and its brachiocephalic branches of the supra-aortic vessels was well demonstrated.

The picture of alternating stenosis and dilatation of the aorta and its branches indicated that despite the early clinical stage the vascular involvement was extensive. Intravascular thrombus formation was a prominent feature. No doubt the turbulent flow within the stenosed arteries brought about the multiple dilatations. The particular pattern of involvement demonstrated by this study should not be interpreted as the only pattern possible. Our study also reveals some interesting features of the dynamics of the circulation and of the compensatory mechanisms involved.[14, 29, 34, 35] Cerebral flows occurred primarily through the vertebral arteries. These vessels showed some dilatation, perhaps due to the extra load caused by gradual obstruction of flow through the carotid arteries.

This form of "aortic arch syndrome" exhibits a characteristic clinical and pathologic picture. It is most common in young women, where symptoms and findings related to insufficient blood flow to the brain, eyes, and arms are usually accompanied by an elevated sedimentation rate. The pathologic features are quite distinctive.

Summary

A case of "idiopathic panarteritis" (Takayasu's disease) of the great vessels in a young Japanese woman is reported and the angiocardiographic studies are presented.

Acknowledgment

For their cooperation in performing the angiocardiographic studies in this case, we are indebted to Drs. T. Nobechi, Chief Radiologist, St. Luke's Hospital; Prof. F. Shimazu and Dr. S. Miura, Radiologists, and Dr. Nakayama, Neurosurgeon, Tokyo Women's Medical College; Prof. K. Sano, Neurosurgeon, Tokyo University Faculty of Medicine was our consultant; all of Toyko, Japan. We are also indebted to Major S. Noguchi and Lt. Col. C. R. Green and the staff of Toyko Army Hospital.

Addendum

Since the preparation of this paper an additional case has been reported in which an angiocardiographic study showed a very similar appearance.[36]

Summario in Interlingua

Es reportate un caso de "panarteritis idiopathie" (morbo de Takayasu) del vasos grande in un juvene femina japonese. Le correspondente studios angiocardiographic es presentate.

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Role of the Kidney in the Pathogenesis of Congestive Heart Failure

By A. Clifford Barger, M.D., Francis P. Muldowney, M.D., and Martin R. Liebowitz, M.D.

"There is an arrangement in the living being, a kind of regulated activity, which must never be neglected, because it is in truth the most striking characteristic of the living being . . ."[1]

FORTUNATELY for the patient with congestive heart failure, the efficacy of the treatment of this disease has surpassed our knowledge of its pathologic physiology. Thus, useful lives have been prolonged despite only fragmentary information concerning the mechanisms responsible for the symptoms of the disease, or the mechanisms of action of the therapeutic regimens and agents employed. The salutory effects of bed rest and digitalis have long been known. More recently, reduction in salt intake coupled with potent diuretics has produced a dramatic improvement in the outlook of the patient with edema and ascites. The potency of the newer diuretic agents has led naturally to a preoccupation with the role of the kidney in fluid retention, as did Withering's original observations on the diuretic action of the foxglove.[2] However, this preoccupation with the late stages of the disease, and with the role of the kidney in the production of edema in congestive heart failure, has tended to obscure the evidence that changes in sodium and water metabolism are present in heart disease at a time when the cardiovascular system is only slightly impaired.[3] These small, important, and early alterations are difficult to evaluate in the human patient, since detailed adequately controlled experiments in the normal state are usually lacking in those patients with heart disease whom the physician wishes to study. Nor is it feasible to do repeated studies in the same individual from the moment that cardiac abnormalities are detected to the time that overt failure appears. Most commonly, observations made during frank congestive heart failure are compared to those made in the same patient following treatment, when the patient, although improved, still does not have normal cardiovascular-renal function. The study of the sequential alterations in function in the natural progressive course of the syndrome would help differentiate the primary changes from secondary abnormalities, and determine whether the changes in sodium metabolism are part of a compensatory process or merely the deleterious effects of circulatory insufficiency. In the constant search for a single mechanism responsible for the sodium retention of congestive heart failure the multiplicity of roles which the sodium ion plays in the body is frequently forgotten. The probability that numerous mechanisms are responsible for the maintenance of normal sodium balance or the alteration of sodium balance in congestive heart failure is rarely stressed. As Weiss and Ellis[4] emphasized many years ago, "evidence is available that a number of mechanisms are responsible for the clinical manifestations of cardiovascular diseases. Confusion exists, nevertheless, because results of experimental and clinical studies of a single aspect of the circulation are still offered as an explanation or index of the multiform nature of circulatory failure." In addition, many critical experiments needed to solve the problem of the pathogenesis of congestive heart failure cannot be performed justifiably in man but can be performed painlessly in the unanesthetized animal under more rigidly controlled and reproducible conditions. Claude Bernard stressed many years ago that in biological science the role of method is even more important than in other sciences, because of the immense complexity

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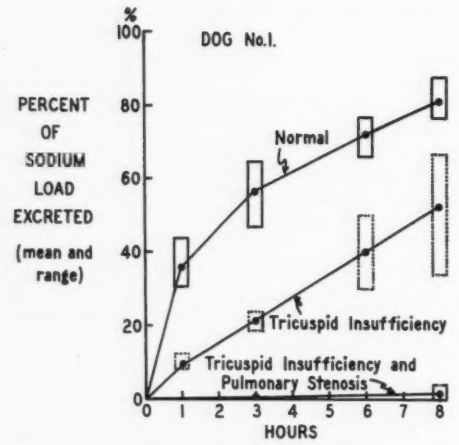

FIG. 1. Cumulative excretion of sodium in the same dog (mean and range) after intravenous infusion of 500 ml. of isotonic saline given from –10 min. to 0. *Top curve:* normal control (3 observations). *Middle curve:* after tricuspid insufficiency (3 observations). *Lower curve:* after combined tricuspid insufficiency and pulmonary stenosis with the development of congestive failure (4 observations). (*Reproduced by permission of the Am. J. Physiol.*[3])

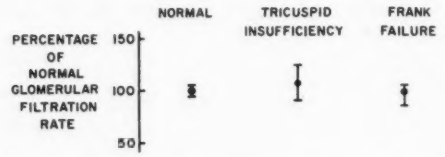

FIG. 2. Summary of changes in basal creatinine clearance (mean and range) in the same 5 dogs in the normal state, after tricuspid insufficiency, and after superimposed pulmonary stenosis and the development of frank failure.

of the phenomena and the countless sources of error which complexity brings into experimentation.[5]

We have tried to develop technics for the production of progressive cardiac impairment in dogs and have shown that the various stages in the progression of heart disease can be duplicated in the laboratory by the production of discrete, right-sided valvular lesions of increasing severity.[6, 7] These surgical operations result in alterations in cardiac function that can be graded from mild to severe, and that have remained constant for months. For example, surgically induced pulmonary insufficiency is associated with insignificant changes in right atrial pressure at rest or during exercise and produces no detectable changes in exercise tolerance. Tricuspid insufficiency, which imposes a greater circulatory stress, leads to an elevated right atrial pressure, with a further rise during exercise, and a slight drop in basal cardiac output, but does not produce signs of overt congestive failure. The combination of tricuspid insufficiency and pulmonary artery stenosis results in a syndrome of chronic, right-sided congestive failure similar to that seen in man. This is characterized by cardiac enlargement, elevated right atrial pressure, low fixed cardiac output, inability to exercise, and retention of salt and water with ascites and edema.

Although gross clinical evidence of sodium retention (i.e., ascites and edema) is first noticed in the dog with frank failure (tricuspid insufficiency and pulmonary stenosis), slight but definite alterations in sodium excretion can be detected even with the mildest of these valvular lesions, that is, pulmonary insufficiency.[3] Following recovery from the operation in which this lesion is produced, the dogs show a slight but persistent reduction in the rate of sodium excretion following an intravenous infusion of isotonic saline. This decrease in sodium excretion occurs in an animal with normal venous pressure and normal basal glomerular filtration rate.[8] Such evidence suggests that alterations in peak capacity for sodium excretion may be a far earlier concomitant of cardiac impairment than is now supposed. Increasing the severity of cardiac damage (tricuspid insufficiency or tricuspid insufficiency plus pulmonary stenosis) produces a progressive decrement in the rate of sodium excretion following saline infusion (fig. 1). Although the animal with tricuspid insufficiency has a reduced ability to excrete a sodium load and has an increased total exchangeable sodium,[9] ascites and edema do not develop. Moreover, the basal glomerular filtration rate may be normal even in the animal with frank congestive failure (tricuspid insufficiency and pulmonary stenosis) (fig. 2). Although the rise in creatinine clear-

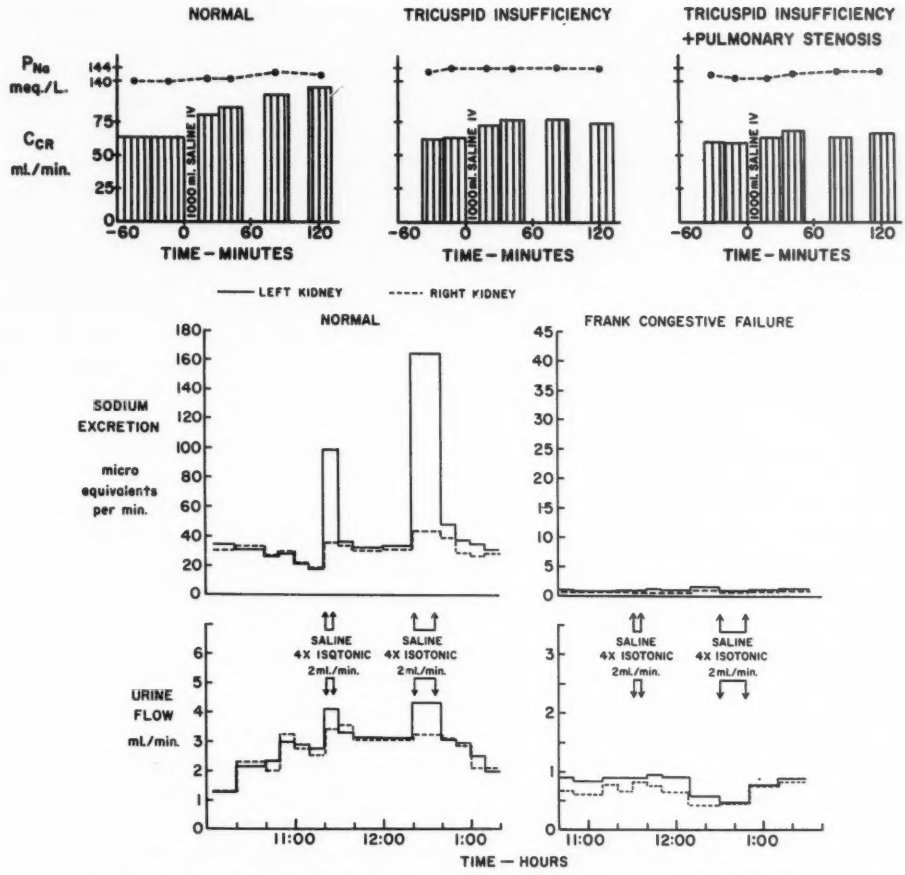

FIG. 3 *Top.* Basal glomerular filtration rate and changes in rate produced by the intravenous infusion of 1,000 ml. of isotonic saline in a 20-minute period in the same dog in the normal state, after tricuspid insufficiency, and after superimposed pulmonary stenosis.

FIG. 4 *Bottom.* Effect of infusion into one renal artery of hypertonic saline (3.5 per cent) on sodium excretion and urine flow in (1) normal, unanesthetized dog, and (2) in unanesthetized dog with congestive heart failure. (*Reproduced by permission of Metabolism.*[11])

ance after infusion becomes progressively smaller as the severity of the cardiac damage is increased (fig. 3), only with the later deterioration of the clinical condition of the animal does the basal glomerular filtration rate fall significantly. At this late stage, in both man and dog, the low glomerular filtration rate probably enhances the sodium retention. However, the finding of a normal basal glomerular filtration rate in the dog with marked ascites and edema strongly suggests that increased tubular reabsorption of sodium is of considerable importance in the sodium retention of congestive heart failure.

To obtain more convincing evidence of increased tubular reabsorption of sodium in congestive heart failure, a method has been developed in this laboratory by Rudolph et al.[10] for chronic catheterization of one renal artery with collection of urine from each kidney separately. The presence of a catheter in the renal artery has not altered renal function over a period of months, and the technic has enabled us to study the effects of sodium

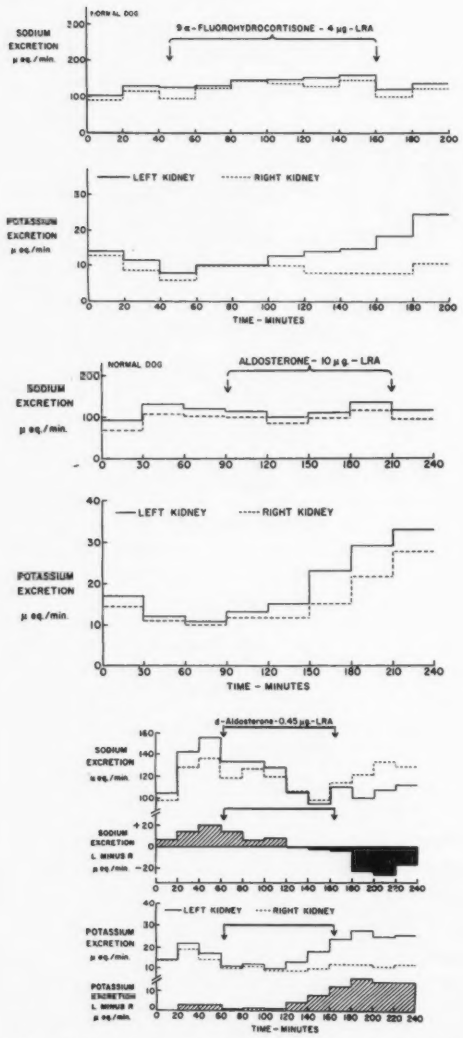

FIG. 5 *Top.* A representative example showing the effect of infusion into the left renal artery (LRA) a 9-α-fluorohydrocortisone (4 μg.) on sodium and potassium excretion in the normal unanesthetized dog. (*Reproduced with permission of Endocrinology.*[22])

FIG. 6 *Middle.* A representative example showing the effect of infusion into the left renal artery of d-aldosterone (10 μg.) on sodium and potassium excretion in the normal unanesthetized dog. (*Reproduced with the permission of Endocrinology.*[22])

FIG. 7 *Bottom.* Effect of infusion into the left renal artery of d-aldosterone (0.45 μg.) on sodium and potassium excretion in the adrenalectomized animal. Differences between the left and right kidney in sodium and potassium excretion are indicated by *cross-hatching* (positive) and *solid black* (negative).

chloride solutions injected directly into the renal artery of a trained, unanesthetized dog. If, in such an animal, a hypertonic solution of sodium chloride (3.5 per cent) is injected for even a short period (e.g., 2 to 5 minutes at the rate of 2 ml. per minute), the sodium excretion of the injected kidney (fig. 4) rises many fold with little or no change in sodium excretion in the opposite kidney. Furthermore, the increased excretion of sodium occurs without change in glomerular filtration rate or renal plasma flow. On the other hand, a similar unilateral, intra-arterial infusion of hypertonic saline has no effect on sodium excretion in a dog in frank congestive failure with marked fluid retention.[11] This absence of effect in the dog with overt failure is observed even though glomerular filtration rate is normal, and hence while an increased filtered load of sodium is presented to the kidney tubules. Such observations offer strong evidence of increased tubular reabsorption of sodium in dogs with congestive heart failure.

Following the work of Merrill[12] emphasis was placed on the role of the reduced glomerular filtration rate in the pathogenesis of the sodium retention of congestive heart failure. Other reports soon indicated that filtration rate was not reduced invariably in patients with heart failure, and that clinical improvement, with increased elimination of salt and water and loss of edema, occurred in patients without any rise in the depressed glomerular filtration rate.[13] Later, with the isolation and identification of a potent salt-retaining hormone in the amorphous fraction of adrenal cortical extract, and with the demonstration of increased sodium-retaining activity in urine extract from edematous patients with congestive heart failure, emphasis was placed on aldosterone secretion and the role this steroid might play in the increased tubular reabsorption of sodium in congestive heart failure.[14] More recent investigations, however, in larger series of patients with congestive heart failure, have failed to show that urinary aldosterone is elevated in all such edematous patients. Muller et al.[15] have suggested that the increased aldosteronuria may be the result, in

part, of the dietary sodium restriction. Moreover, it is hazardous to imply that an increased urinary excretion of aldosterone necessarily indicates hypersecretion from the adrenal cortex. Chart and associates[16] and Yates and co-workers[17] have shown that the rate of destruction of aldosterone is markedly reduced by passive congestion of the liver. Thus, urinary excretion of the steroid may be elevated without increased secretion from the adrenal cortex. It has also been shown that in the normal individual only about 1 per cent of an injected dose of aldosterone is recovered in the urine, and that the errors of the analytical methods are not inconsiderable.[18]

The actual secretion of aldosterone from the adrenal glands of dogs with congestive heart failure has been measured in 2 laboratories, but with opposite results. Davis et al.[19] have reported increased aldosterone secretion in such animals, while Driscol et al.[20] have found no increase in aldosterone secretion. These conflicting observations may indicate that the rate of secretion from the adrenal cortex varies at different stages of the disease, for Driscol et al. made their observations soon after the production of heart failure, whereas the observations of Davis et al. were made later in the disease.

Although the mineralocorticoids have long been known to play an important role in the maintenance of normal sodium balance, the direct renal effect of the steroids has not been shown. Loeb et al.[21] have suggested that the adrenal steroids control extracellular sodium by regulating the renal excretion of sodium. The development of a technic of chronic catheterization of the renal artery mentioned above has enabled us to study the effects of the intrarenal infusion of 9-α-fluorohydrocortisone and aldosterone in the unanesthetized dog (figs. 5 and 6).[22] With the normal animal maintained on a constant intravenous infusion of isotonic saline, and excreting 100 to 150 μEq. of sodium per minute from each kidney, the intrarenal infusion of 4 μg. of 9-α-fluorohydrocortisone over a 2-hour period produced no effect on sodium excretion on the infused side. A unilateral kaluresis was observed on the infused side, however, with the potassium excretion on the left increasing in stepwise fashion above that on the right, which remained relatively constant. Intrarenal infusion of 10 μg. of aldosterone (fig. 6) similarly had no effect on the rate of sodium excretion in the normal dog, but did have a definite effect on potassium excretion. In this latter experiment sufficient aldosterone apparently spilled over into the systemic circulation to produce a kaluresis on the right side as well, which was less than that observed on the infused or left side in any given period.

Since we were unable to demonstrate the antinatriuretic effect of aldosterone or of 9-α-fluorohydrocortisone by intrarenal infusion in the normal dog, dogs that had been used in studies of the normal state were bilaterally adrenalectomized. Desoxycorticosterone and cortisone therapy were withdrawn 4 and 3 days respectively prior to the experiments. Figure 7 illustrates results obtained following infusion of 0.45 μg. of aldosterone into the left renal artery of an adrenalectomized animal. Prior to the intrarenal infusion of aldosterone, sodium excretion on the left side was uniformly higher than that on the right, and this was consistently the case in control studies in this dog. During the intrarenal infusion, and for at least 2 hours thereafter, this relationship was reversed. In the overnight specimen the sodium excretion on the left was again higher than that on the right. The unilateral kaluretic effect was also present and quantitatively similar to that observed in the same dog before adrenalectomy. The changes in sodium and potassium excretion in the adrenalectomized animals occurred without alteration in glomerular filtration rate, again indicating the direct tubular effect of the steroid. These observations on the direct renal effect of aldosterone on potassium excretion and lack of effect on sodium excretion in the normal animal may explain the kaluresis seen in primary hyperaldosteronism and the absence of edema formation in most of these patients.

The lack of effect of intrarenal aldosterone on sodium excretion in animals with intact

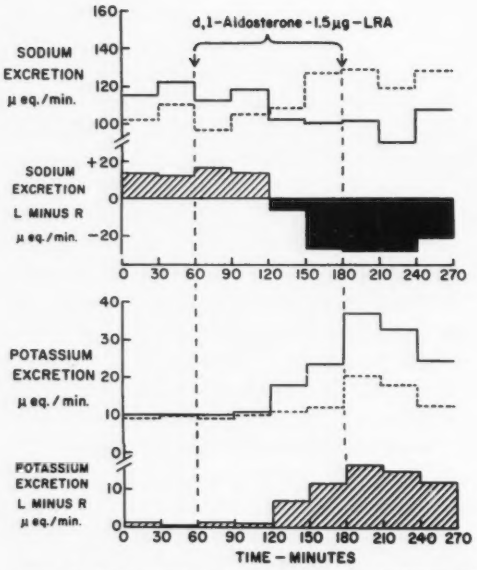

FIG. 8. Effect of left intrarenal artery infusion of d,l-aldosterone (1.5 µg.) on sodium and potassium excretion in the dog with tricuspid insufficiency. (Right atrial pressure = 11 to 12 cm. saline.) The activity of the synthetic d,l-aldosterone used in these experiments is only one half that of the natural isomer used in the experiments illustrated in figures 6 and 7. Differences between the left and right kidney in sodium and potassium excretion are indicated by *cross-hatching* and *solid blacks.*

adrenal glands raised some questions about the possible role of aldosterone in the sodium retention of congestive heart failure, for these animals also have intact adrenal glands. Deane and Barger[23] have observed that the zonae glomerulosae of the adrenal glands from dogs with congestive heart failure were markedly hypertrophied. Moreover, a significant degree of hypertrophy was noted in the dogs with tricuspid insufficiency alone that were without frank edema. These findings suggested increased secretory activity of the zona glomerulosa, the area from which aldosterone is believed to be liberated.[24] Because of these observations, aldosterone was infused directly into the renal artery of dogs with valvular lesions of the heart (fig. 8). Surprisingly, the dog with tricuspid insufficiency responded in the same manner as the adrenalectomized dog. There was decreased sodium excretion and increased potassium excretion on the infused side. In the control periods, sodium excretion on the left exceeded that on the right by 12 to 15 µEq. per minute, while potassium excretion on the 2 sides was equal. In the third period after the start of the intrarenal infusion of aldosterone, sodium excretion on the left fell behind that on the right and remained 20 to 30 µEq. per minute lower. Potassium excretion on the left side rose at the same time. There was presumably some spillover of aldosterone to the right side. Thus, at an early stage of circulatory impairment the response of the kidney to aldosterone is altered in such a fashion that a direct renal effect on sodium excretion can now be demonstrated. The antinatriuretic effect is similar to that observed in the adrenalectomized animal, but not in the normal animal. The inference might be made that the animal with valvular heart disease has relative adrenal insufficiency, but as has been indicated, there is evidence of increased activity of the zona glomerulosa. Whether other hormones from the adrenal gland, or from other sites, may play a modifying role in the sodium retention of congestive failure is still to be determined.

Speculation has long existed concerning the possible role of the renal nerves in the alterations of renal function in congestive heart failure. The function of the renal nerves, however, is a very confusing area of renal physiology. As Smith has pointed out,[25] this chapter in renal physiology begins with Claude Bernard's observation that sectioning the splanchnic nerve in an anesthetized animal resulted in an increased urine flow on the operated side. Bernard attributed this diuresis to increased renal blood flow, although he had no actual measurements of the renal circulation. In 1908 Burton-Opitz and Lucas inserted a stromuhr into the renal vein of animals and confirmed the existence of the vasoconstrictor fibers to the kidney in a direct fashion. Later Marshall and Kolls[26] demonstrated that in anesthetized animals, both acute and chronic denervation of the

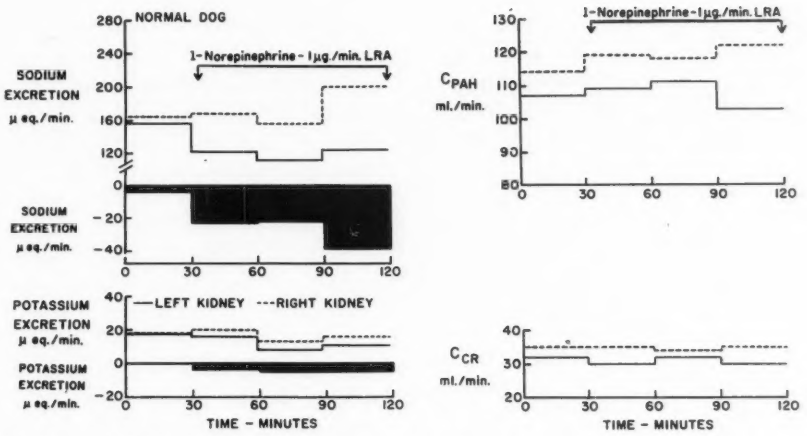

FIG. 9. Effect of left intrarenal artery infusion of l-norepinephrine (1 μg./min.) on sodium and potassium excretion, creatinine (C_{CR}) and para-aminohippurate (C_{PAH}) clearances in the normal dog. Differences between the left and right kidney in sodium and potassium excretion are indicated by *solid black*.

kidney led to an increased chloride excretion on the denervated side without any change in creatinine excretion. In light of our present knowledge of the measurement of glomerular filtration rate with creatinine, the observations of Marshall and Kolls suggested that the denervation of the kidney led to a decreased tubular reabsorption of chloride. Berne,[27] however, was able to show the effect of renal denervation only in the anesthetized animal. Smith has summarized his views as follows: "Renal denervation in unanesthetized normal dogs and men does not produce renal hyperemia, the vasoconstrictor pathways being quiescent under basal conditions; nor does renal denervation have any significant effect on the normal urine flow, upon water diuresis, or pituitary antidiuresis."

The possibility that the renal nerves may play a role in the diminished renal blood flow of congestive heart failure was explored by Mokotoff and Ross in 1948.[28] They determined renal plasma flow and glomerular filtration rate in 11 patients with chronic congestive heart failure before and after the induction of spinal anesthesia high enough to block the renal nerves. The blood pressure during anesthesia was maintained with ephedrine. Glomerular filtration rate and renal plasma flow were unaltered by the procedure. They concluded that a neurogenic mechanism is not required for the maintenance of increased tone of the renal arterioles in congestive heart failure. More recently, Brod and Fefjar[29] attempted to block vasoconstrictor tone in the kidney by the intravenous infusion of dibenamine. They observed that the renal plasma flow increased in patients with congestive heart failure, although changes in glomerular filtration rate and electrolyte excretion were rather variable. Berne and Levy[30] were unable in acute experiments to demonstrate any difference in response of the innervated and denervated kidneys of dogs during progressive pulmonary artery stenosis.

Despite the evidence that appeared to minimize the importance of the renal nerves in the control of renal function, we considered that the subject had not been explored adequately, particularly in the animal with cardiovascular damage. Since l-norepinephrine (levarterenol) is thought to be the principal neurohormone liberated from the sympathetic nerve endings, this compound was infused directly

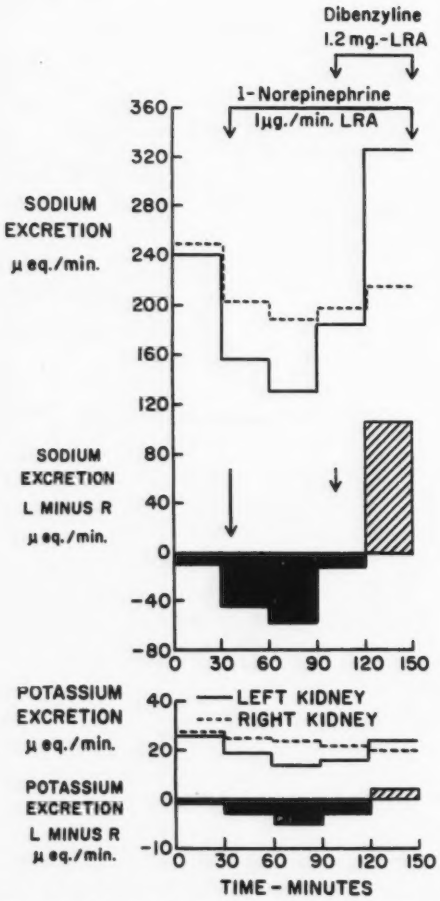

FIG. 10. Effect of left intrarenal artery infusion of l-norepinephrine (1 μg./min.) on sodium and potassium excretion, and reversal of effect with intrarenal infusion of dibenzyline. Differences between the left and right kidney in sodium and potassium excretion are indicated by *cross-hatching* and *solid black*.

into the renal artery of normal dogs at the rate of 1 μg. per minute (fig. 9), giving a renal plasma level comparable to that seen under circulatory stress.[31] In all cases there followed a unilateral drop in sodium excretion and a smaller decrease in potassium excretion. The difference between the 2 kidneys was maintained even after 4 to 5 hours of infusion. Changes in renal flow and glomerular filtration rate were more variable, although there was often a trend toward a unilateral decrease in para-aminohippurate clearance. Infusion of l-epinephrine gave essentially the same results. These effects of intrarenal infusion of l-norepinephrine (or l-epinephrine) were blocked by dibenzyline infused directly into the renal artery (fig. 10). Adrenergic blockade was apparent within a few minutes of the start of the dibenzyline infusion, with a marked increase above normal in sodium excretion on the infused (left) side. Dibenzyline, which blocks both circulating catechol amines and those liberated locally, infused alone into the renal artery of the normal animal in the same dose range had only a very slight effect on sodium, potassium, and water excretion. This suggested that intrinsic sympatho-adrenal tone was not high in the unanesthetized normal dog. In contrast, when dibenzyline was infused into the renal artery of the dog with tricuspid insufficiency (fig. 11), a marked unilateral increase in sodium, potassium, and water excretion was observed suggesting that in this early stage of cardiac impairment there is a definite increase in sympatho-adrenal tone. The unilateral effect produced by dibenzyline persisted for several days following a 1 to 2-hour infusion. The mechanism of the diminished sodium and water excretion has still to be elucidated, for the quantitative separation of changes in tubular activity from alterations in renal hemodynamics remains a difficult problem. The data presently available suggest that dibenzyline often produces an increase in renal plasma flow.

The demonstration of increased sympatho-adrenal activity on the kidney in valvular heart disease raises the question of the nature of the initiating mechanism. Sodium retention is found in a number of diverse conditions in which there is a reduction in effective circulating blood volume and in which there is a tendency toward a decrease in arterial pressure, e.g., hemorrhage, tilting, etc. Under such conditions carotid sinus activity is decreased, leading to a reflex vasoconstriction and restoration of blood pressure. Thus the

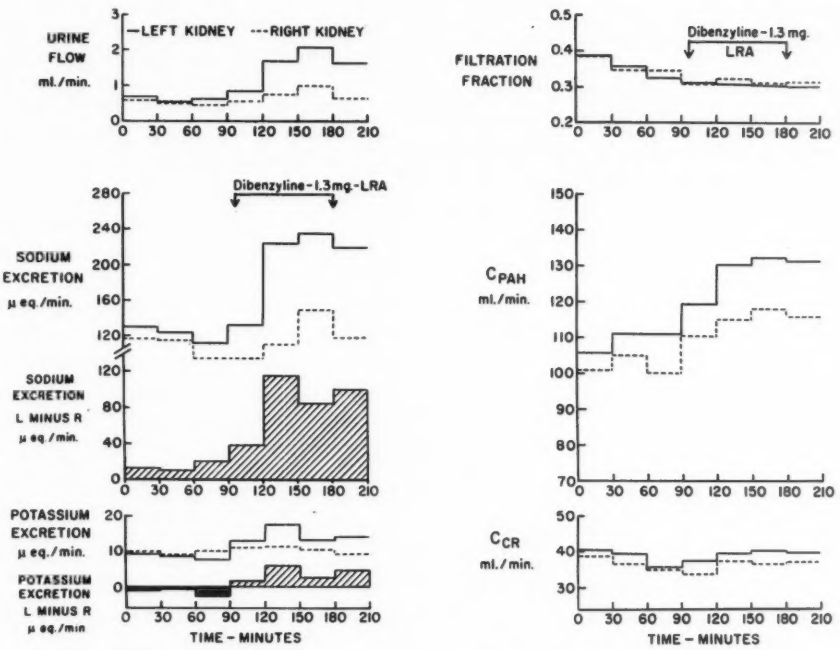

FIG. 11. Effect of left intrarenal artery infusion of dibenzyline (1.3 mg.) on sodium, potassium, and water excretion, creatinine (C_{CR}), and para-aminohippurate (C_{PAH}) clearances in a dog with tricuspid insufficiency. Differences between the left and right kidney in sodium and potassium excretion are indicated by *cross-hatching* and *solid black*.

carotid sinus and the aortic depressor nerves constitute the afferent limbs of a reflex arc, which is of fundamental importance in homeostasis. Impulses pass via these nerves to the vasomotor centers whence efferent impulses travel outward to the heart and blood vessels by way of the sympathetic and vagus nerves. Because of the profound effect that the carotid sinus reflex may exert on the kidney the suggestion was made several years ago[11] that this mechanism may play an important role in the sodium retention of congestive heart failure. However, O'Connor[32] recently reported that decreasing the pressure in the carotid sinus of the unanesthetized animal caused a small increase in sodium excretion. It is important to note in his experiments that clamping the common carotid arteries produced a reflex hypertension. Thus, even though there may have been an increase in renal resistance, renal plasma flow may well have been elevated, accounting for his observations. It must be kept in mind that in the normal reflex activity of the carotid sinus a fall in carotid sinus pressure leads to a decrease in rate of discharge from the organ. The systemic pressure is restored toward normal, but not elevated to hypertensive levels. To circumvent the problem of elevated blood pressure, experiments were devised in which the blood pressure in one kidney was not allowed to rise when the common carotid arteries were clamped. Since, in the dog, the left renal artery arises from the aorta several centimeters caudal to the right, it is possible to place a clamping device around the aorta between the origins of the renal arteries, so that the pressure in the lower or left renal artery can be maintained at normal levels while pressure in the right kidney is allowed to rise with

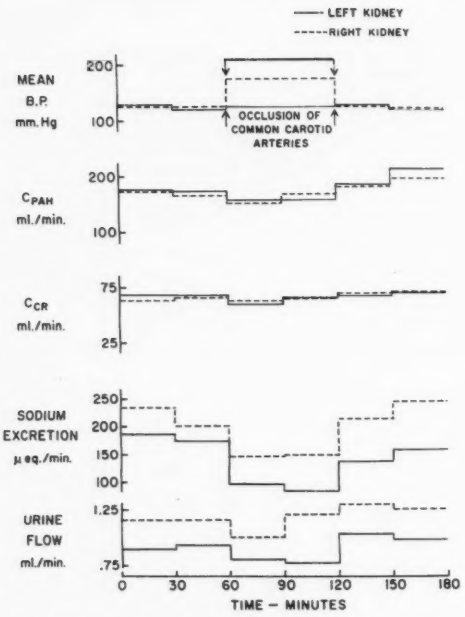

FIG. 12. Effect of occlusion of common carotid arteries of anesthetized dog on glomerular filtration rate, renal plasma flow, urine flow, and sodium excretion. During the period of carotid occlusion the blood pressure in the left kidney was maintained at control level.

systemic pressure when carotid sinus pressure is reduced. In contrast to the findings of O'Connor, reduction in carotid sinus pressure has not led to an elevation of sodium excretion in any of our experiments on anesthetized dogs. In the left kidney, in which normal blood pressure was maintained, sodium excretion fell markedly in all animals, whereas in the right, in which the pressure was allowed to rise, sodium excretion remained constant or fell slightly. In the experiment illustrated in figure 12 compression of the common carotid arteries led to a 50 per cent decrease in sodium excretion on the left, with a slight decrease in urine flow on that side and only minor changes in the creatinine and para-aminohippurate clearances. The decrease in sodium excretion on the right was slightly smaller than that of the left, and the decrease in urine flow was not sustained during the entire period of carotid compression. These observations offer further evidence for the possible role of the carotid sinus as the receptor organ initiating the reflex increase of sympatho-adrenal tone in the kidney in congestive heart failure. Such experiments performed in the anesthetized animal can only serve as pilot studies for further work in the unanesthetized dog. Ultimately one would hope to be able to demonstrate a progressive decline in the rate of discharge of the baroreceptors as one follows an animal through the various stages of cardiac impairment to frank failure.

If there is a progressive decrease in rate of discharge from the carotid sinus with progressive impairment of cardiac function, then a common receptor mechanism may be responsible for both the increased sympathetic activity and for hypersecretion of aldosterone. As was already indicated, it is believed that aldosterone is secreted from the zona glomerulosa of the adrenal cortex, and Deane and Barger have shown that the glomerulosa becomes hypertrophied early in heart disease in the dog. Similar hypertrophy of the zona glomerulosa has been reported by Goormaghtigh and Elaut,[33] Verne and Leger,[34] Coppitz and Cinti[35] and others, following denervation of the carotid sinus in the rabbit and dog. Such denervation interrupted all afferent impulses from the sinus to the vasomotor centers. In addition, Shafer[36] has observed the development of polycythemia with increased blood and extracellular fluid volume in a large percentage of dogs subjected to carotid sinus and aortic arch denervation. Thus, the carotid sinus may regulate mineralocorticoid activity of the adrenal gland as well as sympathomedullary function. Undoubtedly, other mechanisms also play a role in the normal regulation of sodium balance and the sodium retention of congestive heart failure. The availability of animals with progressive cardiac impairment, and the development of new technics for the long-term study of such animals may help to elucidate the interrelationships of these factors in congestive heart failure and other forms of circulatory stress.

Summary

The pathogenesis of sodium retention in congestive heart failure has been a difficult problem to elucidate. The production in dogs of cardiac valvular lesions of increasing severity has enabled investigators to study the sequential alterations in salt and water balance in the same animal from the normal state through the progressive stages of cardiac impairment until frank failure is present. The findings in dogs suggest that: 1. Abnormalities in sodium metabolism are detectable in mild heart disease long before overt failure is present. 2. Total exchangeable sodium may be increased in animals with mild valvular damage. These animals have normal exercise tolerance and normal basal glomerular filtration rates. 3. Increased sympatho-adrenal (adrenergic) activity is responsible, in large measure, for the decreased sodium and water excretion in dogs with cardiac impairment. 4. Preliminary experiments suggest that the carotid sinus may be the receptor organ initiating the reflex increase in sympatho-adrenal tone, and may be the elusive "volume receptor" for which investigators have been searching. 5. Evidence is also available that the carotid sinus may play a major role in the regulation of the zona glomerulosa of the adrenal cortex, the site of aldosterone production.

Acknowledgment

We wish to thank Ciba Pharmaceutical Products for the aldosterone used in these experiments, and Smith, Kline and French Laboratories for the supply of dibenzyline. For observations that have not been reported previously we are indebted to Drs. Richard D. Berlin, G. Octo Barnett, Abraham M. Rudolph, and F. Eugene Yates.

Summario in Interlingua

Le pathogenese del retention de natrium in congestive disfallimento cardiacha essite un problema difficile a elucidar. Le production, in canes, de lesiones del valvulas cardiac de crescente severitate ha permittite al investigatores studiar le alterationes sequential in le balancia de sal e de aqua in le mesme animal ab le stato normal, via le stadios successive del vitio cardiac, usque al declaration de un disfallimento definite. Le observationes in canes suggere que (1) anormalitates del metabolismo de natrium es detegibile in leve casos de morbo cardiac longemente ante le declaration de disfallimento patente, (2) le total del natrium excambiabile pote esser augmentate in animales con leve grados de vitiation valvular, i.e. in animales que ha un normal tolerantia pro exercitio e un normal intensitate del filtration glomerular basal, (3) augmento del activitate sympatho-adrenal (adrenergic) es responsabile in grande mesura pro le reducite excretion de natrium e de aqua in canes con vitios cardiac, (4) experimentos preliminari suggere que le sino carotidic es possibilemente le organo receptori que initia le augmento reflexe del tono sympatho-adrenal e etiam que illo (i.e. le sino carotidic) es possibilemente le elusive "receptor de volumine" que le investigatores ha tentate trovar, e (5) il etiam existe observationes que pare indicar que le sino carotidic ha un rolo major in le regulation del zona glomerulose del cortice adrenal que es le sito del production de aldosterona.

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Movat, H. Z., More, R. H., and Haust, M. D.: The Diffuse Intimal Thickening of the Human Aorta with Aging. Am. J. Path. **34**:1023 (Nov.-Dec.), 1958.

Sections that appeared to be grossly normal were obtained from 92 human aortas at necropsy. The structure and development of the diffuse intimal thickening of the aorta were then classified and carefully examined. Aortic thickening increases with age; is more marked in the distal rather than in the proximal portions of the aorta; is found to undergo only slight individual variation during the first 3 decades of life; and is composed of an intima with 1, 2, or 3 layers, a musculo-elastic layer, a hyperplastic elastic layer, and a connective-tissue layer. The diffuse thickening of the aorta is a result of the normal aging process; focal arteriosclerotic lesions may be superimposed on the thickened aorta. The authors believe that aortic thickening is not a part of the arteriosclerotic process but it undoubtedly represents 1 of the local factors that predispose the aorta to the inception of arteriosclerotic changes.

Karpman

PANEL DISCUSSION

What's New in Arrhythmias?

The Panel was comprised of the following members: HERRMAN L. BLUMGART, *Boston, Mass.*, MODERATOR; W. PROCTOR HARVEY, *Washington, D. C.*; R. BRUCE LOGUE, *Atlanta, Georgia*; MAURICE SOKOLOW, *San Francisco, Calif.*; and E. GREY DIMOND, *Kansas City, Kans.* The Panel Discussion was conducted at the Thirty-first Scientific Sessions of the American Heart Association held at San Francisco, Calif., on Friday, October 24, 1959.

MODERATOR HERRMAN L. BLUMGART: I turned the title of this panel discussion into a question which I asked each of the panelists. Their replies formed a list of 27 subjects. Some were about new agents or new methods of treatment, others had to do with new types of evidence concerning old problems. The first subject will be on "Multiple Sounds in Ventricular Tachycardia—A New Auscultatory Aid in the Bedside Diagnosis," by Dr. Harvey.

DR. W. PROCTOR HARVEY: I am sure that if most of us looked back on cases of ventricular tachycardia that we have observed, we would remember that they often sounded different from other types of rapid heart action. The reason for this difference is the frequent occurrence of multiple low-frequency sounds, sometimes 5 or 6 in a single cardiac cycle. The mechanism of these multiple sounds appears to be related to wide splitting of the first and second heart sounds plus gallop sounds (atrial and ventricular). A patient having these multiple sounds with ventricular tachycardia is shown in figure 1. After reversion to normal sinus rhythm with quinidine these sounds were absent. On listening specifically for these multiple sounds other cases were found, and on reviewing other cases that we had previously recorded, similar findings concerning the presence of these sounds were found. Figure 2 shows 5 examples of ventricular tachycardia, all illustrating these multiple sounds. The auscultatory clues suggesting ventricular tachycardia previously emphasized are a changing intensity of the first heart sound, slightly irregular ventricular rate, and lack of slowing of the ventricular rate with carotid sinus stimulation. In addition to these important findings, which can be observed on auscultation at the bedside, the hearing of multiple low-frequency sounds can aid in even more rapid suspicion of the diagnosis of ventricular tachycardia. Figure 3 shows 13 examples of tachycardia other than ventricular tachycardia, in which these multiple sounds are not present.

As to the mechanism of these multiple sounds, further light can be shed on the problem by the observation of splitting of heart sounds with right or left bundle-branch block in the presence of congestive failure. In bundle-branch block the second heart sound is generally widely split, and frequently the first heart sound also. If the patient has congestive failure a ventricular diastolic gallop is usually present, and if first-degree heart block (or P-R interval on the longer side) or hypertension is present, atrial sounds may be heard. Figure 4 represents a patient with left bundle-branch block and cardiac decompensation, illustrating the wide splitting of the first and second heart sounds plus both atrial and ventricular diastolic gallops.

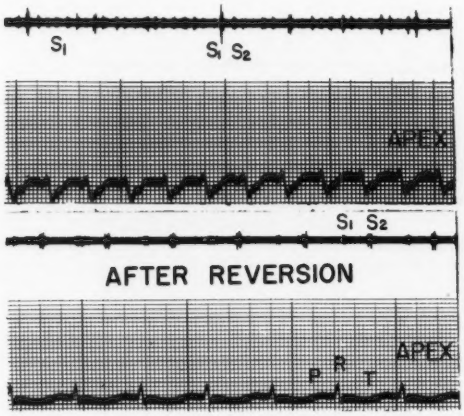

FIG. 1. Male, age 58, several weeks after acute myocardial infarction with ventricular tachycardia (*upper tracing*). Had multiple sounds in addition to changing intensity of first sound (S_1) which were not present immediately after reversion (*lower tracing*).

Our hospital staff has been on the alert for this additional clue to the presence of ventricular tachycardia, and as illustrated by the patient in figure 5, may lead to more prompt recognition and treatment. This 52-year-old man, having pressure in the precordial area of several hours' duration, arrived at the hospital pale, anxious, and with no obtainable blood pressure. Auscultation of the heart revealed a rapid rate of 188. An immediate clue was the presence of multiple low-frequency sounds heard along the lower left sternal border and apex, in addition to a changing intensity of the first heart sound. Slight irregularity of the ventricular rate was present, and carotid sinus pressure produced no slowing. On the basis of these findings procaine amide was immediately ordered to be held in readiness until the electrocardiogram confirmed the diagnosis of ventricular tachycardia. Reversion to normal rhythm occurred after 450 mg. of intravenous procaine amide.

Not every patient with ventricular tachycardia will have these multiple sounds. They are most likely to be present in patients with ventricular tachycardia of longer duration, with wide spread of the QRS complexes, and having congestive failure.

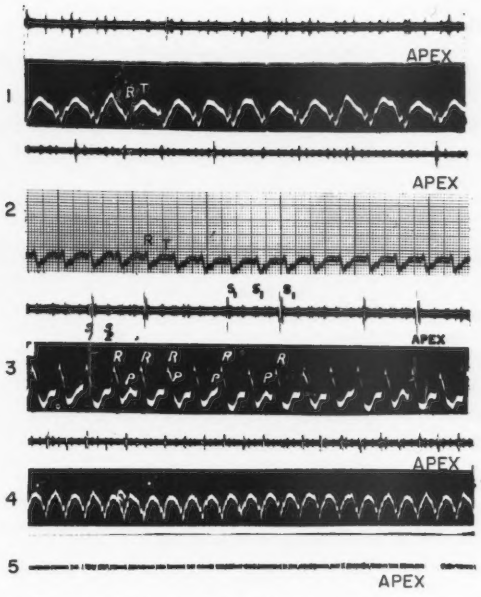

FIG. 2. Tracings of 5 patients, each having ventricular tachycardia. Note multiple low-frequency sounds and changing intensity of first sound (S_1). Lower tracing taken from tape recording.

DR. BLUMGART: Are there any further comments by any of the other panelists?

DR. R. BRUCE LOGUE: I'd like to ask Dr. Harvey if he has ever seen multiple sounds with atrial flutter?

DR. BLUMGART: May I also add to that and make it one package—paroxysmal atrial tachycardia with block?

DR. HARVEY: Yes, we have heard atrial sounds with both atrial flutter and paroxysmal atrial tachycardia with block. These would naturally come up as part of the differential diagnosis, but we utilize the other clinical features; carotid sinus pressure will slow the paroxysmal atrial tachycardia with block, or flutter, and have no effect on ventricular tachycardia.

DR. BLUMGART: The second subject is one that has played an important part in medical literature for some decades. Dr. Sokolow has consented to deal with it, that is to say, "Present Status of Conversion of Chronic Atrial Fibrillation to Sinus Rhythm."

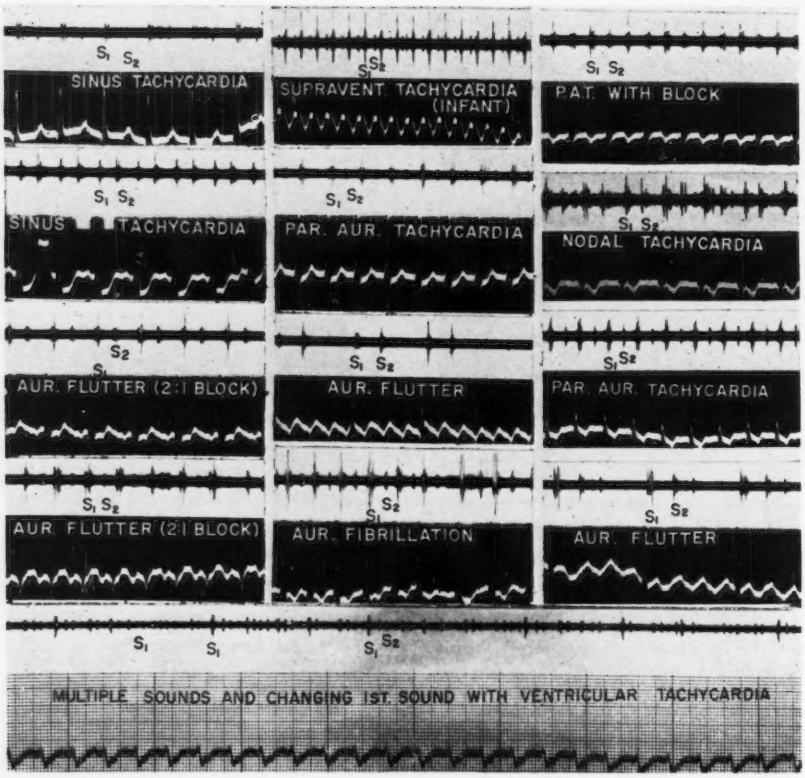

FIG. 3. Tracings of 13 tachycardias. Only ventricular tachycardia (*lower tracing*) shows the multiple sounds in addition to the changing intensity of the first sound (S_1).

DR. MAURICE SOKOLOW: One of the most important things that is new about chronic atrial fibrillation is the appreciation of the fact that artial fibrillation is physiologically undesirable, even though we have seen many elderly individuals who developed atrial fibrillation and who tolerated the arrhythmia reasonably well. Some recent work has shown that with the development of atrial fibrillation, particularly when associated with cardiac failure, the cardiac output fell considerably; when sinus rhythm was restored the cardiac output increased about 30 per cent. Contraction of the atria are important for ventricular filling and for normal cardiac output, particularly in patients who have failure, and therefore individuals who have chronic fibrillation may have progressive enlargement of the heart and may develop chronic cardiac failure.

The influence of atrial fibrillation on the incidence of systemic emboli is well known. There are considerable data in the literature on the point, and perhaps we need not elaborate on it. Patients with atrial fibrillation may be quite uncomfortable, even though they are not in failure, because they may have a rise in ventricular rate that may reach 150 to 160 for the first few seconds or minutes after exercise; this rise in ventricular rate with exercise may occur even though the patient has been digitalized to the point of toxicity. Dr. Blumgart, I think, in the twenties, was one of the first to show this, and recent work has confirmed it. Even though patients have ventricular rates at

rest that are in the range of say 70 to 80, and one would think they were perfectly satisfactorily controlled, their ventricular rate rises considerably with effort. The increased ventricular rate after effort may persist longer in patients who are fibrillating than in patients with sinus rhythm. These patients complained of palpitations, and they are uncomfortable. Because of these 3 difficulties (decreased cardiac output, emboli, and palpitations) we believe that patients with atrial fibrillation are better off if the rhythm can be converted to normal.

If this is true, do we attempt to convert all patients who have chronic atrial fibrillation? The answer is no; primarily because of the fact that conversion of atrial fibrillation with quinidine, which is the only potent drug that can be used for this purpose, is not without hazard. The 2 major hazards are, first, the likelihood of ventricular arrhythmias, rarely, ventricular fibrillation; and secondly, the fact that in a very small percentage of patients, perhaps 0.5 per cent, a systemic embolus may be released following conversion. We have a healthy respect for quinidine, and although we believe that patients are better off with sinus rhythm, we are not unmindful of the fact that whenever we attempt conversion we are accepting a certain risk. Elderly patients, then, who have had chronic atrial fibrillation for some years, who are tolerating the arrhythmia well, and who have no complaints, are usually maintained on digitalis; we usually do not attempt to convert them with quinidine.

The group of individuals whom we attempt to convert can be listed in the following: First, those individuals with fibrillation of short duration, less than 6 months, because of the fact that this group is relatively easily converted and the complications are few; individuals who continue to fibrillate following adequate treatment for thyrotoxicosis usually convert easily, and therefore we attempt conversion in these patients; patients who have had a technically successful mitral valvulotomy and still fibrillate, or who previously had sinus rhythm and then fibrillate postoperatively, usually are given quinidine after a period of 2 weeks or so when everything has stabilized; patients whose ventricular rate is uncontrolled while they are fibrillating, despite full doses of digitalis. These patients may have low-grade, chronic failure, or they may have severe palpitations, and in these patients following conversion to sinus rhythm the ventricular rate may be slow and the patients considerably improved. Lastly, we attempt conversion in patients who have cardiac failure which is not improved despite full treatment of the usual variety. Sometimes, converting to sinus rhythm will be the critical procedure that will relieve the symptoms and signs of cardiac failure.

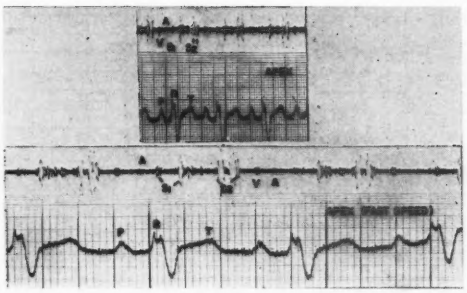

FIG. 4. Patient with left bundle-branch block and congestive failure. Note splitting of first (S_1) and second (S_2) sounds plus atrial (A) and ventricular (V) diastolic gallops.

One should be aware of the patients in whom the most favorable results can be anticipated. In our experience, patients whose fibrillation is less than a year's duration, and particularly less than 6 months' duration, those who have no cardiac failure or considerable cardiac enlargement, and those who do not have mitral insufficiency, usually have the greatest possibility of success, and roughly 85 per cent of these patients will convert with quinidine.

It is important to emphasize that before patients are given quinidine for conversion they should be hospitalized, cardiac failure should be treated, they should be digitalized

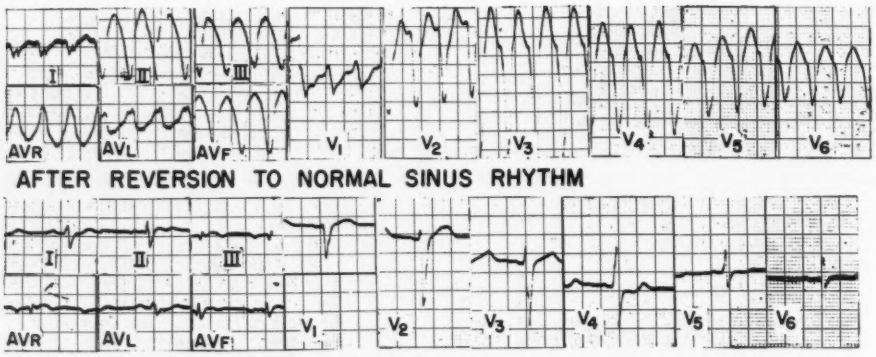

FIG. 5. Male, age 52, with ventricular tachycardia (*upper tracings*). Multiple sounds and changing intensity of first sound were first clues to diagnosis. Reverted to normal sinus rhythm with procaine amide (*lower tracings*).

so that the ventricular rate is slow, and any complication, infection, or nutritional disturbance should be managed first. Quinidine may then be given in moderate doses with close clinical, electrocardiographic, and serum quinidine concentration observations. The dose may be gradually increased, depending upon the tolerance of the patient. We believe that if a patient does not convert following 3 Gm. of quinidine a day, or with a serum concentration of 8 mg. per ml., then the entire situation should be reviewed and a new decision made. One should not use larger doses unless he has had considerable experience with the drug, or unless the clinical condition is sufficiently urgent to warrant a more heroic attempt.

With the careful use of quinidine, and in some instances the combination of quinidine with procaine amide, the majority of patients with chronic atrial fibrillation, who do not have severe failure or fibrillation of long standing, can be converted to sinus rhythm.

I would like to emphasize that we believe the use of quinidine should be likened to an elective surgical procedure, and that the drug should be given only after considerable thought and awareness of its toxicity. It is a very valuable drug, and one must compare the potential therapeutic benefits with the possible risks in deciding whether or not to use it.

One additional point—when moderate doses of quinidine are used, and the patient does not convert, the addition of procaine amide, which by itself is not very effective in producing sinus rhythm, may be successful.

DR. BLUMGART: Would any of the panel like to ask any questions or make any additional comments on this?

DR. LOGUE: Dr. Sokolow, at what level of QRS change will you abandon the administration of quinidine?

DR. SOKOLOW: We believe that moderate widening of the QRS complex that occurs with quinidine is not a toxic manifestation, but is the result of the therapeutic effect of the drug. We usually continue quinidine until the QRS interval exceeds 50 per cent of control value, although we use particular caution when widening exceeds 25 per cent. We arbitrarily stop quinidine at 50 per cent QRS widening, because of the possibility that when QRS widens further that cardiac standstill may occur. In actual practice, we have never seen this occur. We have seen the QRS interval, for example, widen to as long as 0.2 second without the patient's being aware of any particular disturbance; but it has disturbed us.

DR. LOGUE: I should like to ask Dr. Sokolow, also, do you treat those with bundle-branch block?

DR. SOKOLOW: We are very hesitant to use quinidine in patients with bundle-branch block, and our own experience on this is quite limited. Dr. Mervin Goldman of the Veterans Hospital in Oakland, however, has had very good results using quinidine in bundle-branch block and his incidence of toxicity was no greater than that of those who used it in the absence of bundle-branch block. It is possible that the old adage regarding bundle-branch block as a contraindication is unjustified and perhaps should be studied further. I would be considerably more cautious in using quinidine in the presence of bundle-branch block, but if the clinical indication was clear, the block would not deter me.

DR. HARVEY: I would like to mention a couple of "tricks" that have helped us in alleviating the incidence of the toxic gastrointestinal side effects from quinidine. The administration of the drug after meals has helped reduce nausea, and if diarrhea is a problem, Amphojel, probably because of its constipating effects, has been useful (15 to 20 ml. between meals).

DR. BLUMGART: We will go on to the next subject, which is a very important one. I think that the problems we face in this day and age of powerful drugs, which seriously affect electrolytes and the heart itself, are great. As a matter of fact the first paper this afternoon mentioned some of the arrhythmias that occur with chlorothiazide. It is appropriate then that Dr. Dimond will discuss the arrhythmias that occur with various medications such as veratrum, cortisone, hydralazine, reserpine, and so forth.

DR. E. GREY DIMOND: I would like to comment on the subject of mitral valvulotomy and arrhythmias. Here certainly is a circumstance in which a new arrhythmia has occurred. An individual with presently a normal sinus rhythm has a mitral valvulotomy and in the immediate postoperative period has atrial fibrillation. This has been a widely reported observation. Something like one third of the subjects who have normal sinus rhythm prior to mitral valvulotomy develop atrial fibrillation on the first day, sixth day, or ninth day, for example, and in spite of intensive therapy, at least half of them will not revert to normal sinus rhythm. This has been our experience also. In other words, one sixth of all persons who have a normal sinus rhythm prior to a mitral valvulotomy will end with chronic atrial fibrillation. Attempts at conversion during the immediate postoperative period have definite drawbacks and in general it is better to wait a matter of months before trying for conversion.

Other things have occurred in recent years that actually have produced arrhythmias that really did not exist before; not new arrhythmias, but new causes. Hydralazine certainly does produce persistent tachycardia. On the other hand, reserpine produces a bradycardia which, with its slowness and the increased stroke volume of each pulse, often produces a concerned and heart-conscious patient.

Hypothermia, in the immediate postoperative period, presents frequently an arrhythmia due to the dislocation of the cardiac pacemaker. We had 10 consecutive cases of atrial septal repair under hypothermia, and in 8 of these, in the first few days following the chilling episode, there was a shift of the pacemaker into the atrioventricular node.

Still another example of iatrogenic arrhythmia is being seen in the elderly patient. In the well-digitalized patient the addition of compression dressings to the eye may result in excessive bradycardia and even in periods of cardiac standstill.

In the postabsorption period, after a meal rich in glucose, a heavily digitalized patient may actually develop arrhythmias indicating digitalis intoxication. The movement of potassium into the cells and depletion of readily available potassium at the cell membrane are perhaps the provoking causes.

Cortisone in large doses has a tendency to shorten the P-R interval and if potassium loss is high, ventricular arrhythmias may result.

Finally, the Brock procedure, the procedure in which the right ventricle is actually transected and entered, may well alleviate the cause for the right heart overload, but a surprising percentage of these individuals end with right bundle-branch block.

As you look back over the comments I have made, one must note how each new step forward has in turn created its own new hazard.

DR. BLUMGART: Are there any comments or further questions?

DR. SOKOLOW: I think Dr. Dimond's comment that it is unwise to try to convert an arrhythmia in the acute postoperative state is very important. It has been our practice to delay conversion until the patient has convalesced from the mitral valvulotomy and has been stabilized with respect to his activity, diet, nutrition, medication, and so on. Some patients who become toxic with quinidine, if given on the second or third postoperative day, will tolerate the drug at a later time without toxicity and with successful conversion.

DR. DIMOND: There is another characteristic item about the use of quinidine that is not often stressed in teaching: the peculiar experience of gradually increasing the quinidine dosage to full tolerance and to definite toxicity and yet with no success at conversion. When the drug has been stopped and the drug level has been allowed to dissipate, the patient will convert to normal sinus rhythm. This may occur at 6 to 8 hours after the last dosage, for example. I call this the "make or break" phenomenon and I have no reasonable explanation for it.

DR. LOGUE: I would like to comment on a recent patient who was not digitalized and who developed atrial fibrillation in the postoperative period during the infusion of glucose. The intravenous administration of 3.0 Gm. of potassium chloride over a period of 2 hours caused a reversion to normal sinus rhythm.

DR. BLUMGART: Time is going on, and we have so many subjects here that I think we will go right on to the next one, which is the subject proposed by Dr Logue, namely, "The Control of Arrhythmias by Decreasing Thyroid Metabolism."

DR. LOGUE: The usefulness of radioactive iodine in the management of arrhythmia in the patient with thyrotoxicosis is well known. However, its usefulness in the management of recurrent supraventricular arrhythmia in the euthyroid patient is less widely appreciated.

It has been well demonstrated that the production of hypothyroidism by I^{131} may be quite helpful in decreasing the frequency or preventing recurrent attacks of either atrial tachycardia or atrial fibrillation. Dr. Eliot Corday and his co-workers have reported excellent results in a group of 33, 28 having excellent results following such therapy. This treatment should be utilized for those patients who cannot be controlled by customary forms of therapy. It has been useful in patients with normal hearts, in patients who have arteriosclerotic heart disease, and in those with rheumatic heart disease. Occasionally patients with chronic atrial fibrillation will undergo spontaneous reversion to normal sinus rhythm following the production of hypometabolism.

An example of the use of I^{131} is illustrated in figure 6. This patient, 74 years old, had arteriosclerotic heart disease with frequent attacks of angina pectoris, accompanied by congestive failure, and attacks of syncope. These symptoms were not controlled with combinations of procaine amide and quinidine, but following the administration of I^{131} the patient became hypothyroid. The attacks ceased, the patient's angina was greatly improved, heart failure subsided, and over a follow-up period of 1½ years she has been active and free from attacks of atrial fibrillation.

DR. BLUMGART: In our studies of the effect of hypothyroidism induced by I^{131} in the treatment of congestive failure in angina pectoris, we were interested in observing a small group of patients who had been fibrillating, and who had had atrial fibrillation for many years, and we were surprised to

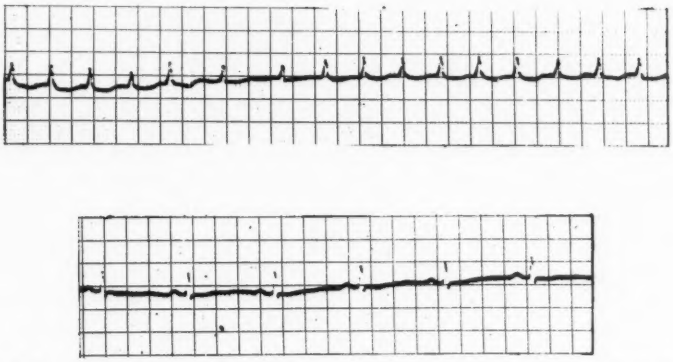

FIG. 6. H.W.B. a 74-year-old woman with frequent disabling attacks of atrial fibrillation (*upper strip*) and angina pectoris. Protein-bound iodine was 4.4 mg. per cent and I^{131} uptake was 26 per cent. I^{131} (20 mc.) was given and there has been no recurrence of atrial fibrillation in 1½ years since hypothyroidism was induced. *Lower strip* shows usual sinus rhythm.

find that when they returned on some occasion after treatment, they had persistent normal sinus rhythm.

In relation to Dr. Logue's comments, it might be interesting to relate some of the experiences of our group, particularly carried out by Dr. George Kurland, Dr. Arnold Golodetz, and Dr. A. Stone Freedberg, which will be reported on Sunday morning. They studied particularly 39 patients in whom the usual parameters of thyroid function were entirely normal, including the protein-bound iodine and clinical signs. However, in about a third of those patients there were 2 abnormalities in regard to thyroid function that were disclosed by further studies, namely, the turn-over of thyroxine in the blood was greatly increased, and the red-blood-cell uptake was greatly increased. These changes were found in about a third of the patients. In the 39 patients studied, 5 patients were favorably influenced by the administration of ordinary stable iodine; all but 2 had normal thyroid function. In 2 of these patients, when the stable iodine was stopped, atrial fibrillation recurred, to be replaced again by normal sinus rhythm when the iodine was resumed. I think a very important practical point in the treatment of some patients with arrhythmias, even though they seem to be entirely euthyroid, is that if you are not going to think of using radioactive iodine in the next 6 to 8 months, it might be worthwhile to try ordinary stable iodine.

DR. LOGUE: Did any of these patients have abnormal protein-bound iodine?

DR. BLUMGART: No.

DR. LOGUE: We have been interested in a group of those who have normal uptakes and normal protein-bound iodine, who have nodules demonstrated by radioactive scanning, and who have responded following administration of I^{131}. Did some of the cases discussed by you have nodules?

DR. BLUMGART: No, not by clinical examination. I say that with reservation because, as we know, there may be small adenomas present on pathologic examination that may not have been disclosed on physical examination.

DR. SOKOLOW: There is one aspect of hyperthyroidism about which I should like to comment. In the development of hyperthyroidism there is a period, sometimes perhaps weeks or months, during which time the usual tests for hyperthyroidism may be negative, only to become positive at a later time. We have seen at least 2 patients with paroxysmal atrial arrhythmias, 1 with fibrillation, and 1 with flutter, in whom we suspected the possibility of an overactive thyroid gland, but all the tests were negative; 6 months later it was obvious that the patients had

hyperthyroidism, and appropriate therapy prevented recurrent attacks of arrhythmia. In addition to the possibility, therefore, that the patient may not show overt hyperthyroidism, he may present himself with paroxysmal atrial arrhythmias during the process of developing thyrotoxicosis.

DR. BLUMGART: I would state in regard to the series that I mentioned, Dr. Freedberg and Dr. Kurland have examined these patients repeatedly.

It is too bad that our time is getting short. We have time for only 2 more subjects. The next one will be discussed by Dr. Harvey, namely, "The Present Treatment and Prevention of Ventricular Tachycardia."

DR. HARVEY: In the treatment of ventricular tachycardia early recognition of the presence of this arrhythmia is most important, as this should be regarded as a medical emergency requiring prompt treatment. The choice of drugs is generally between quinidine or procaine amide. As a rule, procaine amide intravenously is used first and the following precautions are taken: The ampule containing 1 Gm. of procaine amide is diluted to 100 to 125 ml. with 5 per cent dextrose in water. A vasopressor such as Levophed is also available in another solution for intravenous use, if necessary, for any hypotension that develops. The separate solutions of procaine amide and Levophed are connected to the intravenous tubing so that either solution can be stopped or given when necessary. On the opposite arm a blood pressure cuff is attached so that frequent blood pressure determinations may be taken during the infusion. A direct-writing electrocardiograph to enable constant monitoring of the electrocardiogram is also employed. Procaine amide is then started and we attempt to give the 1 Gm. over a period of approximately 30 minutes. If hypotension develops, the procaine amide is stopped temporarily and replaced by the infusion of Levophed. On the other hand, if no hypotension develops, the vasopressor is merely held in readiness. At the first sign of reversion of ventricular tachycardia procaine amide is discontinued. Occasionally, the entire amount may be given without reversion to normal sinus rhythm. If such is the case, before giving an additional amount of procaine amide it is preferable to wait one half to 1 hour, or even longer, as reversion may take place during this period of waiting. If after this period, however, the ventricular tachycardia persists, then an additional gram of procaine amide is diluted in the same manner as described and with similar precautions. As a rule, reversion takes place during the infusion of the first gram of the procaine amide. Once reverted, we have found oral quinidine preferable for maintenance, and generally give 0.3 Gm. at intervals of approximately every 6 hours.

The patient who initially presents with ventricular tachycardia and shock or significant hypotension is first given the vasopressor agent, as we have seen occasional instances in which reversion has occurred merely by elevating the blood pressure, thereby making administration of procaine amide unnecessary. In fact, any type of arrhythmia associated with shock or severe hypotension may possibly be reverted or aided by the initial use of a vasopressor agent.

If ventricular tachycardia is a manifestation of digitalis toxicity, then the use of potassium is indicated with or without additional procaine amide.

Time does not permit a more detailed discussion of the more complicated or resistant types of ventricular tachycardia. The treatment as discussed has, in our experience, proved useful and generally successful.

DR. BLUMGART: The next subject on our program is "The Use of External Electric Current for Cardiac Standstill and Ventricular Fibrillation," which will be taken over by Dr. Logue.

DR. LOGUE: One of the most significant advances in the management of cardiac standstill and arrhythmias such as ventricular fibrillation has been the development of the external cardiac pacemaker and the external defibrillator by Dr. Paul Zoll and

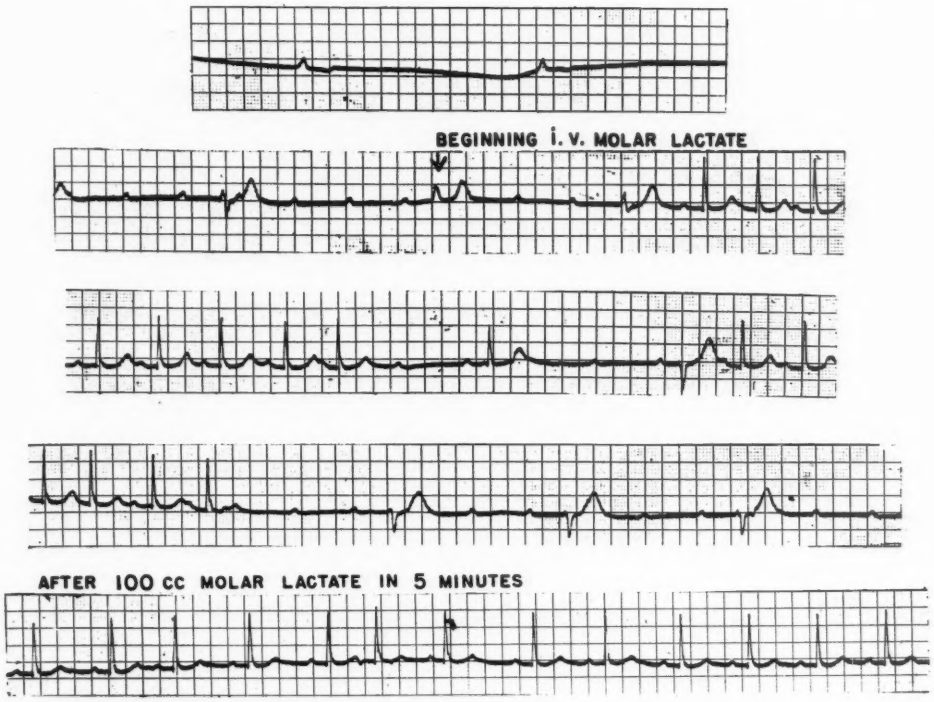

FIG. 7. Effect of molar sodium lactate in increasing ventricular rhythmicity and improving atrioventricular conduction.

his co-workers. It has certainly been life-saving in patients with Stokes-Adams seizures, whether naturally occurring or induced by intracardiac surgery. I think it is most useful in patients with coronary disease in whom cardiac standstill or ventricular fibrillation occurs. Most of the patients who die with rhythm disturbances due to coronary disease do so by standstill rather than by fibrillation. I think it's use is important in every instance of cardiac arrest in which thoracotomy has been done. The patient should be hooked to the stimulator prior to closing the chest and this should be maintained for some days because of the frequency with which recurrent ventricular tachycardia, standstill, and ventricular fibrillation occurs. Its use is valuable when one is using toxic drugs such as quinidine, digitalis, potassium, or procaine amide. The electric stimulator should be available when procedures such as pericardial paracentesis is being done, since ventricular standstill or ventricular fibrillation may rarely occur.

I should like to present 3 cases to illustrate the use of the pacemaker and the external defibrillator. The first of these is a patient with Stokes-Adams disease. The second is a man of 40 with his first myocardial infarction who developed cardiac arrest. The third patient developed ventricular fibrillation due to quinidine therapy.

The first patient, a woman of 74, had coronary arteriosclerosis with angina pectoris and frequent Stokes-Adams attacks. For a time the attacks were controlled by the use of the external stimulator but death ultimately occurred. In many instances, however, the patient may be carried through a critical period of depressed atrioventricular conduction and recovery may ensue. Isoproterenol is frequently useful, given as a constant in-

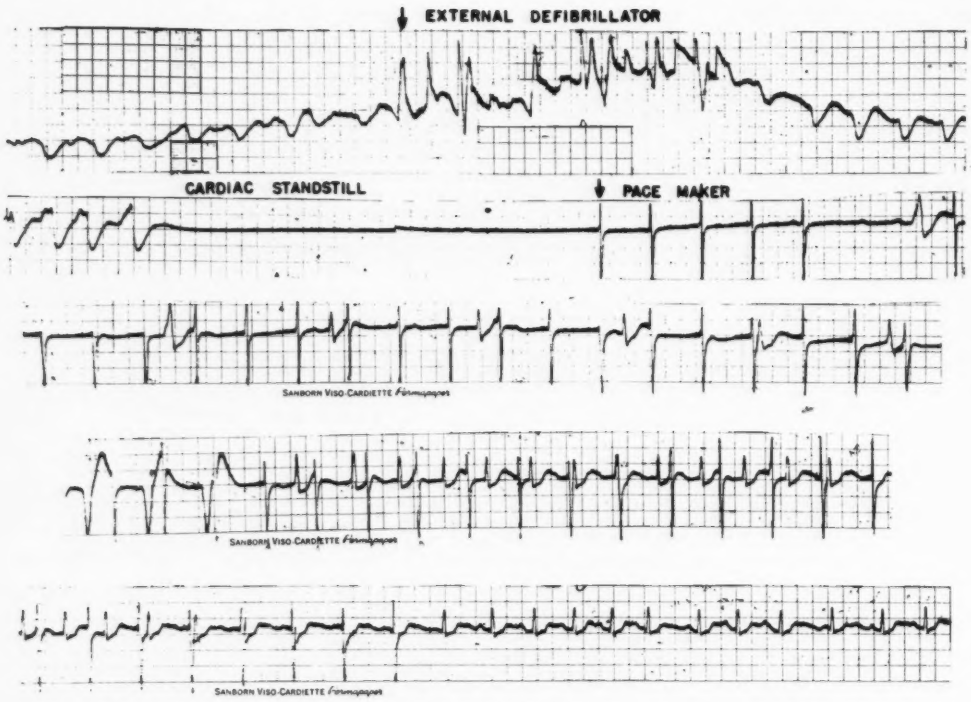

FIG. 8. Ventricular fibrillation, external electric defibrillation, ventricular standstill, external electric stimulation, idioventricular beats, and return of atrioventricular conduction.

travenous infusion or sublingually. The intravenous administration of molar lactate is valuable on occasion and may produce a return to normal atrioventricular conduction; however, its effects are of brief duration (fig. 7).

The second patient was a man of 40 with his first myocardial infarction. He was given procaine amide prophylactically by intramuscular injection because of ventricular premature beats. Approximately 24 hours later he developed sudden cardiac arrest. An intern notified the family of his apparent death but an alert fellow instituted artificial respiration and the cardiac pacemaker, with a return to normal sinus rhythm and complete recovery.

The third patient, a woman of 74, developed chronic atrial fibrillation while taking thyroid extract. Following the administration of quinidine, 0.4, 0.6, and 0.8 Gm. at intervals of 2 hours, conversion to sinus rhythm occurred 6 hours after the last dose. A prophylactic dose of 0.4 Gm. was given but prior to this dose the patient had a convulsive seizure thought to be due to cerebral embolism. Some 14 hours after conversion she began to have ventricular fibrillation with respiratory arrest and continuous convulsive seizures. At this time, her physician, Dr. John Wade of Montgomery, began mouth-to-mouth resuscitation and the use of the external defibrillator. Figure 8 demonstrates selected strips showing ventricular fibrillation, electric defibrillation, and cardiac standstill; external electric stimulator was ineffective at this point, but an intrinsic idioventricular rhythm appeared that was soon followed by normal sinus rhythm. Recovery was uneventful.

Dr. Wade was curious about the sequence of events and upon checking found that the

pharmacist had sent enteric coated quinidine, so that delayed toxic levels were reached well after conversion occurred, some 14 hours after the last dose of quinidine. One should keep in mind the hazards of long-acting quinidine in the conversion of atrial fibrillation, particularly in situations in which absorption is for any reason delayed.

DR. BLUMGART: Are there any comments?

DR. DIMOND: I would like to warn about one very definite hazard from the cardiac monitor and pacemaker in a patient with a recent coronary occlusion. Frequently during the night the electrode contact to the skin will be broken, either through the patient's turning in his sleep or by the electrode paste's drying out. This broken contact will activate the stimulator and the sleeping patient will begin receiving a series of electrical jolts through his chest wall.

DR. BLUMGART: The other point is, you would not have to have it so arranged that the stimulator would go on automatically—just have the auditory signal.

Dr. Zoll tells me that now there have been 200 cases who have been treated successfully by means of the cardiac pacemaker, and he has had personal experience in the defibrillation of 8 patients, including 5 who also had at times paroxysmal ventricular tachycardia, which was also abolished by countershock.

I should like to thank the panelists for their effective presentations.

Wacker, W. E. C., Margoshes, M., Bartholomay, F., and Vallee, B. L.: Bananas as a Low-Sodium Dietary Staple. New England J. Med. **259**:901 (Nov. 6), 1958..

Analyses were reported showing that sodium was a trace element in bananas with the mean sodium content being 0.41 μg./Gm., or approximately 0.002 mEq. per banana—a negligible amount. The variations in sodium content of fruit grown under ordinary conditions were found to be quantitatively insignificant. This data indicated that bananas were suitable as the staple portion of low-sodium diets. Two patients with salt retaining syndromes developed a profound diuresis when placed on a diet consisting of 10 bananas supplemented by 1.5 liters of low-sodium milk. The diet was palatable, nutritious, and well tolerated. It provided 1,980 calories, 62 Gm. of protein, and an average sodium content of 3.02 mEq.

SAGALL

ABSTRACTS

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ATHEROSCLEROSIS

Hauge, J. G., and Nicolaysen, R.: The Serum Cholesterol Depressive Effect of Linoleic, Linolenic Acids and of Cod Liver Oil in Experimental Hypercholesterolaemic Rats. Acta physsiol. scandinav. **45**: 26, 1959.

A comparison was made of the cholesterol depressive effects of linoleic and linolenic acids and of cod liver oil in rats made hypercholesteremic by the authors' technic of feeding 10 per cent coconut oil and 1 per cent cholesterol. Cod liver oil and a furfurol fatty acid fraction of this oil markedly depressed the serum cholesterol. Considerable reductions in serum cholesterol were also obtained with the unsaturated fatty acids. The number of double bonds may be a decisive factor. Linolenic acid had a stronger action than linoleic.

RINZLER

Hauge, J. G., and Nicolaysen, R.: A Rapid Method for the Study of the Effect of Unsaturated Fatty Acids on Cholesterol Metabolism in Rats. Acta physiol. scandinav. **45**: 19 1959.

The authors describe a method for the simultaneous production of essential fatty acid deficiency and hypercholesteremia in young rats. Pregnant mothers and the litters born were given a diet containing 10 per cent hydrogenated coconut oil and 1 per cent cholesterol. The young rats grew approximately at a normal rate the first 4 weeks of life. In the next 50 days weight increase slowed down and very high liver and plasma cholesterol values resulted, together with various symptoms of essential fatty acid deficiency. At this stage the rats were divided into groups receiving daily for 2 weeks 20 to 100 mg. of polyenoic acids or fats rich in these acids. The total serum cholesterol was determined in each rat at the start of the experimental diet, and again after 14 days. Control studies were run contemporaneously. This resulted in falls of the serum cholesterol level of up to 50 per cent or more. With the aid of partial hepatectomy at zero day, a substantial reduction of liver cholesterol was also seen to follow the administration of polyenoic acid.

RINZLER

Raut, V. S., Fish, C. A., and Pincus, G.: Biosynthesis of Cholesterol in Animal Blood. Proc. Soc. Exper. Biol. & Med. **99**: 534 (Nov.), 1958.

This study reports the in vitro biosynthesis of cholesterol from radioactive acetate in animal blood. There was a decisively positive incorporation of C^{14} labeled acetate into cholesterol in samples of calf and pig blood; more in the calf than in the pig blood. Cholesterol synthesized in rat, rabbit, cow, and piglet blood samples had by comparison a very low level of radioactivity.

KRAUSE

Kuo, P. T., Whereat, A. F., and Hodwitz, O.: The Effect of Lipemia upon Coronary and Peripheral Arterial Circulation in Patients with Essential Hyperlipemia. Am. J. Med. **26**: 68 (Jan.), 1959.

Six patients with essential hyperlipemia were studied to correlate the changing serum lipid with the subjective and objective evidence of cardiac and peripheral ischemia. Five of the 6

patients had evidence of coronary artery disease and 1 had intermittent claudication. Large changes in the serum triglyceride levels could be induced by fat free, full, or high fat diets. In a given patient, subjective and objective findings of arterial insufficiency occurred with the change in plasma lactescence and serum triglyceride levels. No critical serum lipid level was found at which all patients developed clinical signs. Two patients with coronary disease had arterial oxygen saturations of 92.1 and 92.5 per cent in lipemia which rose to 95.8 and 96.1 per cent after clearing of lipemia. A positive electrocardiographic exercise test was performed in 5 patients while triglycerides were high. After clearing, subjective improvement in angina and an improved electrocardiographic response to exercise were noted. Response to standard or "claudication time" test was similarly improved on reduction of lipids. Improvement of the ballistocardiogram was also noted in 1 treated patient. Heparin was ineffective in clearing the plasma and did not produce significant improvement of the ballistocardiogram, electrocardiographic exercise response, or claudication time.

KURLAND

Chapin, M. A., and Proger, S.: The Distribution of Lipid and Phospholipid in Paper Electrophoresis of the Serum Lipoproteins in Normal Subjects and in Patients with Atherosclerosis. J. Lab. & Clin. Med. 53: 39 (Jan.), 1959

Changes in the phospholipid content of the serum beta lipoproteins in normal subjects and in those with atherosclerosis were studied in groups divided as follows: young men and women with no family history of diabetes or hypercholesteremia; an older group normal by the usual examinations; a group comparable to the older aged group but who had had recent episodes of myocardial infarction and were in their recent recovery phase at the time of testing; and patients with uncomplicated diabetes mellitus, nephrosis, essential hypercholesteremia, and myxedema. Determinations of serum cholesterol, phospholipids, tryglycerides, total lipids in the serum, and total lipid and phospholipid in each of the 2 lipoprotein fractions were made. The sera of young women contained more alpha lipid and less alpha phospholipid than was found in the sera of young men, while the young men's sera had greater amounts of beta lipids but less beta phospholipids than the young women. In the group of normal older persons, increased beta lipid and phospholipid were found, with the former being disproportionately increased; less alpha lipid and phospholipid was present in this group than in the sera of young women. No sex difference in the distribution of these lipids was detected in this group of older people. In persons with known coronary atherosclerosis there was greater proportion of total lipid in the beta fraction than was true in the normal subjects, while both the alpha lipids and alpha phospholipids were decreased. There was an increase in both the lipids and phospholipids of the beta lipoprotein fraction in coronary atherosclerosis with a disproportionate increase in the amount of lipids when compared with phospholipids. Similar findings were noted in the small groups of diabetic, nephrotic, essential hypercholesteremic, and myxedemic patients.

MAXWELL

BLOOD COAGULATION AND THROMBOEMBOLISM

Sass, M., O'Connell, D. J., and Bovarnick, M.: Coagulation of Blood. Effect of Calcium-Binding by Glutamyl Peptide Polymer. Am. J. Clin. Path. 31: 26 (Jan.), 1959.

Studies with a number of plasma expanders have shown that some of these compounds may interfere with coagulation of blood as measured by in vitro tests. Glutamyl peptide polymer is another plasma expander and its effect on blood coagulation was measured by a number of tests. In all experiments the branched chain glutamyl peptide polymer was added to human plasma or freshly drawn human blood. A calcium-binding effect by this polymer was demonstrated by equilibrium dialysis experiments as well as by interference with various steps in the sequence of blood coagulation. These effects were overcome by the addition of 10 mg. of calcium per gram of polymer. Studies on blood containing 50 per cent expander solution and the added calcium showed no interference with those agents of coagulation requiring calcium.

KAYDEN

CONGENITAL ANOMALIES

Loogen, F., Rippert, R., Santa Maria, E., and Wolter, H. H.: Anomalies of the Great Systemic and Pulmonary Veins. II. Communication. Ztschr. Kreislaufforsch. 48: 136 (Feb.), 1958.

Isolated partial transposition of the pulmonary veins with termination in the inferior vena cava was found in 3 patients; this anomaly could be recognized roentgenologically, and was also characterized by bronchial anomalies and smaller size of the right hemithorax. Partial pulmonary

vein transposition combined with other anomalies was found in 39 patients; of these, atrial septal defect was present in 29, corresponding to 21 per cent of all patients subjected to surgery for septal defect. A direct diagnosis can be made if the cardiac catheter enters 1 of the transposed veins, but transposition becomes probable if blood oxygen analysis shows a considerable left-to-right shunt with only a minor pressure gradient between the 2 atria. The blood flow in the veins can be determined directly by injecting dye into them and determining the dye concentration in arterial blood.

LEPESCHKIN

Gonin, A., Lagadou, and Froment, R.: Incomplete Aortic Rupture in Marfan's Syndrome (With Reference to a Personal Case of Dissecting Hematoma). Arch. mal. coeur. 51: 1105 (Dec.), 1958.

A 36-year-old woman with lenticular ectopia, arachnodactyly, flat feet, and kyphoscoliosis, who had previously had spontaneous penumothorax, suddenly felt severe pain radiating into the teeth. A diastolic aortic murmur was heard soon afterward. A pericardial friction rub appeared on the next day, and the electrocardiogram showed elevated T wave in V_2-V_6 and an elevated S-T segment in V_2. Angiocardiography showed marked dilatation of the sinus of Valsalva and moderate aortic coarctation. After 1 month marked left ventricular dilatation and an electrocardiographic pattern of left ventricular strain appeared. This condition was stable after 10 months. Among 16 members of the patient's family, 7 died suddenly when still young.

LEPESCHKIN

Evans, W.: Faults in the Diagnosis and Management of Cardiac Pain. Brit. M. J. 1: 249, 1959.

Chest pain is a common symptom and naturally always raises the suspicion of a cardiac diagnosis. Many causes for chest pain other than a cardiac origin are known and dyspepsia is a particularly common source. For proper interpretation a careful history, physical examination, and properly interpreted electrocardiogram are essential. In this respect the author pays particular attention to a triple heart rhythm and also cites electrocardiographic signs that might be forerunners of subsequent myocardial infarction. The invalidism from cardiac-like pain erroneously diagnosed can be considerable. Once cardiac infarction has occurred and recovery has taken place, rehabilitation is in order. In order to accomplish this properly it is important for the physician to guide his patient. This can be accomplished by frank discussions with the patient and his spouse. When possible, the patient should be returned to his previous occupation after a suitable period of time. In the event of recurrent pain proper instruction in the use of glyceryl trinitrate is necessary. Reassurance and encouragement by the physician can help cardiac patients adjust to their life after myocardial infarction.

KRAUSE

Gürtler, R., Weber, J. W., Müller, P., Sahli, H. R., and Cottier, H.: Peculiarities of the Ebstein Syndrome. Ztschr. Kreislaufforsch. 48:30 (Jan.), 1959.

In the first patient, in whom tricuspid displacement was proved by cardiac catheterization, the only abnormality was intermittent pre-excitation (Wolff-Parkinson-White syndrome) in the electrocardiogram; the normal QRS complexes showed marked left axis deviation and deep Q waves in V_{5-6}. This patient had frequent attacks of paroxysmal tachycardia with a pattern of right bundle-branch block. The second patient showed a prolonged P-R interval and right bundle-branch block, a holosystolic murmur and an extra sound 0.12 second after the second sound; at autopsy a combination of marked tricuspid displacement with a high ventricular septal defect and pulmonary stenosis with regurgitation was found. The third patient showed at autopsy a combination of slight tricuspid displacement, reduplication of the mitral ostium, and aortic coarctation with a persistent ductus originating distal to the point of stenosis.

LEPESCHKIN

Char, F., Adams, P., Jr., Anderson, R. C.: Electrocardiographic Findings in One Hundred Verified Cases of Ventricular Septal Defect. J. Dis. Child. 97: 48 (Jan.), 1959.

The electrocardiograms of 100 children with proved isolated ventricular septal defects were analyzed by using a system of ratio values in order to allow comparison of mixed-age data; in addition, the tracings were analyzed by conventional methods and by the system of overloading patterns. The authors found only slight correlations between electrocardiographic values and physiologic (pulmonary artery pressures, pulmonary flow) or histologic (pulmonary vascular changes) data. No typical electrocardiographic pattern was recognized but right ventricular hypertrophy was present in the majority of cases, was commoner among older patients, and tended

to occur with low pulmonary blood flow and high pulmonary artery pressures. The presence of deep Q waves and upright T waves in V_6 appeared to indicate a good prognosis for surgery, and a higher than normal T wave in V_1 with a lower than normal T wave in V_6, a poor prognosis.

KARPMAN

Moss, A. J., Adams, F. H., and O'Laughlin, B. J.: Congenital Malformation of the Cardiac Conduction System. J. Dis. Child. **97**: 72 (Jan.), 1959.

A case is reported of a 5-year-old girl with congenital interruption of the cardiac conduction system diagnosed during life and unassociated with other cardiac defects. The authors point out that congenital heart block may be present both in patients with gross anatomic defects of the heart and in patients with only microscopic lesions in the conduction system. They emphasized that the distinction is extremely important, since the prognosis and management are so vastly different. When the conduction defects are complicated by gross anatomic abnormalities, the prognosis is quite variable, depending upon the associated anomaly, and surgical intervention may be indicated; patients with the isolated conduction defect require no treatment and the prognosis is probably very good. The authors propose a reclassification of the nomenclature by offering the term "congenital malformation of the cardiac conduction system, with or without associated gross cardiac defects."

KARPMAN

Crittenden, I. H., and Linde, L. M.: Pulmonary Hypertension and Vascular Change in Patients with Congenital Heart Disease. J. Dis. Child. **97**: 202 (Feb.), 1959.

The pertinent literature concerned with pulmonary hypertension and pulmonary vascular changes in patients with congenital heart disease is reviewed. The consensus is that increasing pulmonary vascular resistance serves a protective function at first but progression of the anatomic vascular changes may eventually be very detrimental to the patient.

KARPMAN

Campbell, M.: The Genetics of Congenital Heart Disease and Situs Inversus in Sibs. Brit. Heart J. **21**: 65 (Jan.), 1959.

An analysis of 2,000 families with a case of congenital heart disease revealed 40 families (2 per cent) in which there were 2 or more examples of a congenital heart lesion. The malformations were the same or similar (concordant) in most of the 22 acyanotic pairs and only 2 pairs had different (discordant) lesions. There were 8 pairs where both members were cyantoic and 10 where 1 was cyanotic and 1 acyanotic. Discordant lesions were more common in this cyanotic and mixed pair group. The defects were concordant more often when siblings were involved than when a parent and child were involved. The author suggested that the frequency with which 2 congenital heart lesions in a family were of the same nature favored a genetic rather than an environmental factor, and the data appeared to be compatible with recessive inheritance. Although it was not very common for 2 children with congenital heart disease to be born in 1 family (2 per cent incidence), when there was 1 child in the family with a congenital heart lesion subsequent children showed such a malformation more often than would be expected by chance.

PAUL

CONGESTIVE HEART FAILURE

Gold, H., Greiner, T., Kwit, N. T., Otto, H. L., and Warshaw, L.: Effect of Digitalis and Diuretics on Exertional Dyspnea. J.A.M.A. **169**: 229 (Jan. 17), 1959.

Ninety-three ambulant patients without atrial fibrillation were chosen from a total of 204 patients with the diagnosis of congestive heart failure because their main problem was exertional dyspnea. They lacked physical signs of congestion and they had no manifest complicating factors that might cause dyspnea. About three fourths of these individuals were in older age groups with arteriosclerotic or hypertensive heart disease. They were studied for control of exertional dyspnea with digitalization and diuretics. They were treated with various courses, each for a period of several months: digitalization alone, placebo tablets, a diuretic alone (meralluride sodium by intramuscular injection), and combined therapy with the diuretic and digitalization. It was evident that there was a variant of exertional dyspnea most clearly seen in patients with chronic heart disease with few or no physical signs of congestion, uninfluenced by digitalis but frequently brought under some degree of control by diuretic therapy. The suggestion was made for a therapeutic test to detect those in whom prolonged treatment with diuretics should be pursued and a similar test to detect patients now commonly subjected to long treatment with digitalis in whom there was little prospect of beneficial results.

KITCHELL

Brest, A. N., and Likoff, W.: Hydrochlorothiazide in the Treatment of Congestive Heart Failure. Am. J. Cardiol. 3: 144 (Feb.), 1959.

Hydrochlorothiazide in oral doses of 50 to 150 mg. daily was added to a standard treatment program for congestive heart failure in 20 patients, in 12 of whom failure had been refractory to therapy. Sixteen patients responded well within a few days, 2 responded partially, 1 did not improve, and 1 had to discontinue the drug because of nausea. In each patient, the serum chloride level decreased slightly; but no change was noted in other serum electrolyte levels, in blood urea nitrogen values, in peripheral blood cell counts, or in routine urinalyses. It was concluded that hydrochlorothiazide appeared to be a very potent diuretic agent with minimal side effects.

ROGERS

CORONARY ARTERY DISEASE

Senderoff, E., Kavee, D. J., Johnson, R. J. R., and Baronofsky, I. D.: Survival Following Acute Coronary Artery Ligation Subsequent to Irradiation of Canine Heart. Proc. Soc. Exper. Biol. & Med. 100:1 (Jan.), 1959.

Based on the premise that repeated small doses of radiation will produce dilatation of existing capillaries and precapillary arterioles, the hearts of dogs were irradiated. Four to 6 days following the last treatment ligation of the anterior descending branch of the left coronary was accomplished. There were 2 groups of controls; 1 in which after ligation defibrillation was not attempted and the other in which defibrillation was used. There were also 2 groups that were radiated: 1 with 1,300 r and the other with 2,000 r. Based on the data presented the mortality rate in the radiated group was considerably lower. The ability to defibrillate radiated dogs successfully was also strikingly evident. Presumably these results were accomplished by creating increased myocardial vascularity.

KRAUSE

Ruegsegger, P., Nydick, I., Freiman, A., and LaDue, J. S.: Serum Activity Patterns of Glutamic Oxaloacetic Transaminase, Glutamic Pyruvic Transaminase and Lactic Dehydrogenase Following Graded Myocardial Infarction in Dogs. Circulation Research 7:4 (Jan.), 1959.

Experimental myocardial infarction induced by coronary ligation in the dog was followed by increased serum activity of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and lactic dehydrogenase. No alterations in these enzyme activities were noted following reversible, transient electrocardiographic changes of injury and ischemia. Infarcts as small as 1 Gm. in size resulted in significantly increased serum activity, and the peak elevations in serum activities are crudely proportional to the size of the infarct. Measurement of the enzyme activity in infarcted and normal myocardial tissue as well as in coronary sinus blood suggested that the increases in serum enzyme activity were the result of leakage from the damaged myocardium.

PAUL

Günter, F.: Clinical Aspects of Myocardial Infarction. Arch. Kreislaufforsch. 29: 107 (Dec.), 1959.

A series is reported of 369 patients (286 men) with a new, major myocardial infarction treated in the period 1947 to 1957. In men, the incidence of myocardial infarction was greatest in the sixth decade: in women, it kept increasing with age. No infarctions were noted in women under 40. Mortality within the first 3 months of the attack was 23.8 per cent; anterior wall infarction resulted in a slightly higher mortality than those of the posterior wall. Mortality increased with age. The most frequent cause of death was myocardial insufficiency. Next in frequency were ventricular fibrillation, acute circulatory collapse, thromboembolic complications, and reinfarction. Cardiac rupture did not play a significant role. Of 84 necropsied cases, 65 showed coronary sclerosis with thrombosis, 18 coronary sclerosis without thrombosis. Only 1 patient showed no severe sclerosis. The symptoms after the onset of infarction had a certain prognostic significance. Ominous signs were ventricular tachycardia, myocardial insufficiency immediately after occurrence of infarction and severe collapse. The supervention of failure at a later period has lesser significance on life prognosis. The influence of other diseases (hypertension, diabetes), occupation, body weight, family history, and seasons were discussed.

BRACHFELD

Walker, R. S., Watson, E. C., and Watt, J. K.: Incidence of Coronary Ischemia after Partial Gastrectomy. Brit. M. J. 2: 1438 (Dec. 13), 1958.

It is generally conceded that the incidence of coronary artery disease is low when the intake of animal and unsaturated fats is low. After the Polya operation for gastrectomy, I^{131} labeled fats are excreted more rapidly and there is also

diminished absorption of a fatty meal. This impaired fat absorption could be reflected in a lower incidence of coronary artery disease in gastrectomized patients. Forty patients who had undergone Polya type gastrectomies were compared with 40 "normal" male subjects and 40 additional patients with duodenal ulcers. In order to evaluate the presence of coronary artery disease the Master double 2-step test and blood lipoproteins were studied with particular reference to their beta:alpha ratio. Evidence was presented that demonstrated a significantly lower incidence of coronary ischemia in long-term gastrectomized patients when compared with "normal" and "ulcer" controls. This fact could not be related to lowering of the beta:alpha lipoprotein ratio nor to changes in the pre-beta lipoprotein. Furthermore, this study confirmed the fact that (by the method of evaluation used) there was no increase in the incidence of coronary artery disease in "ulcer" patients compared with the "normal" individuals. Although the gastrectomized patients were much lighter as a group, there was no direct relationship between weight and ischemia as demonstrated by the Master test.

KRAUSE

Gill, T. J., III, McBride, R. A., and Dammin, G. J.: Coronary Embolism. Report of Three Cases. Am. Heart J. **56**: 878 (Dec.), 1958.

Three cases of embolism to the left coronary artery with death resulting from myocardial infarction are reported. In 1 patient the embolus arose from a vegetation of bacterial endocarditis, in the second, from a thrombus in the atrium; and in the third, from atheromatous deposits in the proximal aorta. Since these 3 patients were observed over a period of about 4 months, the authors believe that coronary embolism occurs more commonly than has been found in the past and will be found more often with careful gross and microscopic autopsy study.

SAGALL

PHARMACOLOGY

Beyer, K. H.: Nonmercurial Organic Diuretics. Arch. Int. Med. **102**: 1005 (Dec.), 1958.

Fundamental actions of a number of nonmercurial diuretic agents and their therapeutic application are described. Urea and mannitol are examples of compounds that act as osmotic diuretic agents by withholding from reabsorption an approximate osmolar equivalent of water. The xanthine diuretics act primarily by inhibiting the renal tubular reabsorption of sodium and chloride. The diuretic effect probably is secondary to the saluretic action. Theophylline, the most frequently used of the xanthine group, is considered a rather weak diuretic. Mictine and Rolicton are representatives of the pyrimidinediones and aminouracil derivatives. Their mode of action is like xanthines. The renal tubules contain substantial amounts of carbonic anhydrase. Acetazolamide (Diamox) acts as a carbonic anhydrase inhibitor. It induces a natriuresis which is generally associated with a marked increase in potassium and bicarbonate excretion, and an increase in urinary pH. It is noteworthy that acetazolamide does not cause an increase in chloride excretion of any consequence. The role of aldosterone in the pathogenesis of fluid retention associated with cirrhosis, nephrosis, and perhaps hypertensive cardiovascular disease has recently been emphasized. Therefore, there has been recent interest and experiment in the development of aldosterone antagonists. Spirolactones are now under investigation as an approach to the regulation of electrolyte and fluid excretion by antagonizing aldosterone. The exact mode of action of chlorothiazide (Diuril) as a diuretic is not clear. In general, it appears to be intermediate in its pharmacodynamic characteristics between acetazolamide and the organomercurial diuretic agents. This drug at present seems suitable for the therapy of numerous classes of edema. It is a potent saluretic and the physician must be aware that hypokalemia may occur under the combined conditions of enthusiastic salt restriction and high, maintained dosage of chlorothiazide.

KRAUSE

PHYSICAL SIGNS

Berg, H. H.: Bedside Criteria for the Diagnosis of Intracardiac Thrombi by Carotid Auscultation. German M. Monthly **3**: 320 (Oct.), 1958.

Four patients are presented in whom a left-sided intracardiac thrombus could be suspected by auscultation over the right carotid artery using a stethoscope with a small bell and carefully avoiding any pressure. In 2 patients a rough and constant systolic murmur was heard and autopsy showed polypoid or racemose thrombotic masses arising from a cusp of the aortic valve. In 1 patient with myocardial infarction a peculiar drumming staccato noise was detected over the base of the heart and the carotid arteries, particularly over the right. The unusual character of the noise led to the suspicion of an intracardiac flapping thrombus in the area of infarction and this was confirmed at postmortem examination. In a fourth patient, also shown at autopsy to have a mural thrombus, a similar noise was detected over the carotid arteries and the base of the heart.

SAGALL

PHYSIOLOGY

Spitzbarth, H., Weyland, H., and Gersmeyer, E. F.: Accidental Systolic Murmurs and Velocity of Flow in the Pulmonary Artery. Ztschr. Kreislaufforsch. **47**: 965 (Nov.), 1958.

In 8 normal persons the mean velocity of blood flow in the pulmonary artery was measured by means of a catheter bearing a heated thermistor on its tip. Epinephrine increased this velocity, whereas norepinephrine and hypertensin decreased it. As these drugs had the same effect on the intensity of physiologic systolic murmurs in the pulmonic region, these murmurs were considered to be caused by turbulence in the pulmonary artery and the outflow tract of the right ventricle.

LEPESCHKIN

Deavers, S., Smith, E. L., and Huggins, R. A.: Critical Role of Arterial Pressure During Hemorrhage in the Dog on Release of Fluid into the Circulation and Trapping of Red Cells. Am. J. Physiol. **195**: 73 (Oct.), 1958.

Anesthetized dogs were divided into 3 groups and bled as follows: the first group was bled a mean of 16 per cent of the original blood volume; the second group was bled to 50 mm. Hg arterial pressure (mean bleeding volume 26 per cent, range 9 to 34 per cent); the third group was bled to 35 mm. Hg arterial pressure (mean bleeding volume 49 per cent, range 29 to 70 per cent). Pressures were maintained for 30 minutes in the last 2 groups before measurements of red cell and plasma volumes were made. Red cell volume was measured using radioactive Cr^{51} and plasma volume with radioactive I^{131}. In the first group in which there was no change in arterial blood pressure, the measured and the expected cell and plasma volumes were in acceptable agreement. In the second group, there was also reasonable agreement between the measured and the expected cell and plasma volumes but the standard errors were large, indicating the variability in the physiologic response to hemorrhage by individual dogs. The measured and expected cell and plasma volumes of dogs bled 49 per cent of their initial blood volume (held at 35 mm. Hg pressure) was not in agreement after either the hemorrhage or reinfusion. The standard errors in this group were small, indicating a relatively uniform response to this degree of hemorrhage and blood pressure. An arterial blood pressure of 50 mm. Hg appears to be a critical pressure in the dog for the operation of the compensatory mechanisms involved in the release of fluid into the circulation and for the trapping of red cells.

KAYDEN

Abramson, D. I., Kahn, A., Rejal, H. Turman, G. A., Tuck, S., Jr., and Fleischer, C. J.: Relationship between a Range of Tissue Temperature and Local Oxygen Uptake in the Human Forearm. II. Changes Observed after Arterial Occlusion, in the Period of Reactive Hyperemia. J. Clin. Invest. **37**: 1039 (July), 1958.

The results of this study demonstrate that a temperature-oxygen uptake relationship exists for the magnitude of the oxygen debt developed during arterial occlusion and subsequently repaid during reactive hyperemia. Repayment of oxygen debt involved primarily an increase in local circulation, with oxygen removal from the blood playing a secondary role.

WAIFE

Szabo, G., Magyar, S., and Solti, E.: Pharmacologic Effects on the Coronary Arterial Flow after Acute Experimental Occlusion. Ztschr. Kreislaufforsch. **47**: 971 (Nov.), 1958.

In dogs the flow through the descending branch of the left coronary artery was measured with a rotameter after partial occlusion of this branch. Intravenous injection of papaverine, euphyllin (aminophylline), sodium nitrite, or chlorpromazine caused no appreciable change in coronary flow or a slight transient increase followed by a marked decrease as a result of arterial hypotension. When the drugs were injected into the coronary artery, the initial increase was slightly greater, but ventricular extrasystoles and sometimes ventricular fibrillation appeared in the case of papaverine, euphyllin, and chlorpromazine. The electrocardiographic changes caused by coronary occlusion were not altered. Intravenous or intracoronary injection of strophanthin did not affect coronary flow but intensified the electrocardiographic changes and caused ventricular extrasystoles or fibrillation. Norepinephrine always caused elevation of blood pressure and a secondary increase in coronary flow, but had no effect on the electrocardiogram.

LEPESCHKIN

Kardesch, M., Hogancamp, C. E., and Bing, R. J.: The Effect of Complete Ischemia on the Intracellular Electrical Activity of the Whole Mammalian Heart. Circulation Research **6**: 715 (Nov.), 1958.

The authors reported the effects of complete ischemia on the spontaneous ventricular action and resting potentials recorded from the ventricular cells of the isolated dog or rabbit heart in a modified Langendorff preparation. Spontaneous membrane action potentials persisted for 20

minutes following the cessation of coronary perfusion. The earliest change in the configuration of the action potential was a decrease in its duration due to a shortening of the depolarization phase. These changes were followed by a progressive fall in the amplitude of the action potential spike and the resting membrane potential fell to an average of 65 per cent of the control value. The findings in the anoxic cell were believed to be related to damage in the membrane ionic transport of sodium and oxidative phosphorylation mechanisms.

PAUL

Nowy, H., and Frings, H. D.: Correlation between Stroke Volume and Central Blood Volume in Persons with Normal Hearts. Ztschr. Kreislaufforsch. **47**: 986 (Nov.), 1958.

In 30 persons with normal hearts under basal conditions Evans blue dye was injected into the cubital vein and blood samples were taken from the brachial artery of the other side. The stroke volume calculated from the dye-dilution curve was on the average 70 ml. at a calculated central blood volume (minute volume times circulation time) of 1,500 ml. and 110 ml. at a volume of 3,000 ml.; the correlation coefficient between these 2 values was +0.64. The 50 per cent and 90 per cent limits for this relationship were calculated statistically. The correlation to the stroke volume was more significant than to the minute volume. It is concluded that abnormal variations of the heart output and stroke volume can be recognized better if they are correlated to the central blood volume.

LEPESCHKIN

Holmes, R., and Rasch, P. J.: Effect of Exercise on Number of Myofibrils per Fiber in Sartorious Muscle of the Rat. Am. J. Physiol. **195**: 50 (Oct.), 1958.

The number of myofibrils per fiber at 7 different cross-sectional levels of the right sartorius muscles of exercised rats was compared with the number of myofibrils per fiber of the right sartorius muscles of unexercised control animals. Exercise was performed daily for 7 weeks by the experimental group. No statistically significant differences were observed in the number of fibers, weight of muscles, or weight of the animals. A greater variation in the number of myofibrils per fiber was noted in the exercised animals than in the control animals, and there appeared to be an increased number of myofibrils per fiber at both ends but not in the center of the muscles of the exercised group.

KAYDEN

Bisset, G. W., and Lee, J.: Antidiuretic Activity in the Blood after Stimulation of the Neurohypophysis in Man. Lancet **2**: 713 (Oct.), 1958.

The antidiuretic activity in peripheral blood during inhibition of water diuresis was measured after stimulation of the neurohypophysis by smoking cigarettes and amyl nitrite. Thirty-five, 57, and 259 milli-units of antidiuretic substance (ADS) were excreted in the urine after smoking, whereas none could be found during the recovery period. In all 3 subjects studied, ADS was present in the blood after, but not before, smoking. Smoking did not inhibit diuresis in 2 experiments and produced only a moderate inhibition in a third, indicating the unreliability of nicotine in smoking as a test of neurohypophysis function. Inhalation of amyl nitrite in 1 subject caused inhibition of diuresis but antidiuretic activity could not be detected in either the blood or urine.

KURLAND

Abramson, D. I., Kahn, A., Tuck, S., Jr., Turman, G. A., Rejal, H., and Fleischer, C. J.: Relationship between a Range of Tissue Temperature and Local Oxygen Uptake in Human Forearm. I. Changes Observed under Resting Conditions. J. Clin. Invest. **37**: 1031 (July), 1958.

Local heating and cooling affected oxygen uptake in the resting forearm. These changes were dependent upon alterations in local blood flow, with the mechanism of oxygen removal from the blood playing a secondary and dependent role. Raising the local temperature of tissues in vivo increased the resting oxygen uptake; cooling did the reverse. These results fit in with in vitro and other experimental observations.

WAIFE

Haddy, F. J., Scott, J., Fleishman, M., and Emanuel, D.: Effect of Change in Flow Rate upon Renal Vascular Resistance. Am. J. Physiol. **195**: 111 (Oct.), 1958.

These studies focus upon the mechanism of increased renal resistance that is associated with increments in arterial pressure. Changing renal blood flow rate in anesthetized laparotomized dogs showed that resistance decreased and then increased as a function of renal flow rate. The onset of the increase in resistance was more dependent upon flow rate than arterial pressure. These relationships were unaltered by section of renal nerves, infusion of phentolamine, infusion of phentolamine and eserine, and ventilation with 20 per cent carbon dioxide. Elevation of arterial pressure failed to elevate greatly the flow rate of renal lymph. It was suggested that the increase

in renal resistance resulted from arterial vasoconstriction initiated by some local mechanism which was independent of nerves, circulating adrenalin, carbon dioxide tension and hydrogen ion concentration. The mechanism could be activated by a change in flow rate.

KAYDEN

Dermksian, G., and Lanb, L. E.: Cardiac Arrhythmias in Experimental Syncope. J.A.M.A. **168:** 1623 (Nov.), 1958.

Since significant cardiac arrhythmias, some of which were associated with syncope, have been found to occur during various experimental respiratory maneuvers, studies were performed on 50 healthy young male aviation cadets, all of whom initially denied previous syncopal episodes. Observations of blood pressure and pulse were made both at rest and during 15-minute orthostatic tolerance tests on the tilt-table while various breathing maneuvers were performed. The latter included breath-holding at maximum inspiration, prolonged breath-holding, hyperventilation, and breath-holding after hyperventilation. Carotid sinuses were massaged during the study for 15 seconds. When the subjects were assured of anonymity, 30 per cent admitted to previous syncopal episodes; and during the experimental procedures 42 per cent had one or more syncopal or near syncopal episodes associated with significant cardiac arrhythmias in approximately three quarters of the instances. Twenty-four of the subjects developed syncope associated with the breathing maneuvers. Of the 15 cadets who admitted to previous syncope approximately one half developed experimental syncope and 14 of the remaining 35 who denied previous syncope lost consciousness during the study. Seventy-four of the subjects developed some form of cardiac arrhythmia during the experimental procedures. Carotid sinus massage induced this in 16 per cent, respiratory maneuvers in 56 per cent, and orthostatic stress in 10 per cent. Thirty cases in which respiratory maneuvers induced arrhythmias received 1.2 mg. of atropine and 6 minutes after injection in no instance could any arrhythmia be induced by the breathing maneuvers. It is concluded that many pilots at the beginning of their flight training have experienced syncope, but this does not necessarily represent an underlying disease state and these cases could not be definitely identified by the experimental procedures. It is believed that the same efferent reflexes are stimulated by stretch reflexes in the lung and by carotid sinus pressure so that atropine protects against the development of arrhythmias produced by respiratory maneuvers, perhaps by abolishing vagal reflexes.

FREEDBERG

Carlsten, A., Folkow, B., Grimby, G., Hamberger, C. A., and Thulesius, O.: Cardiovascular Effects of Direct Stimulation of the Carotid Sinus Nerve in Man. Acta Physiol. scandinav. **44:** 138, 1958.

Direct stimulation was made of the carotid sinus nerve of 5 men whose nerve was exposed during operations for cancer of the neck. Pulse rate, blood pressure, and pulse amplitude were continuously recorded from an indwelling catheter introduced into the left brachial artery and connected to a strain-gage manometer. Definite reflex responses were obtained at low stimulation rates, with maximal effects around 40 to 60 impulses per second. A reflex bradycardia and a blood pressure fall with a decreased pulse amplitude were obtained. Concomitantly, a marked fall in resistance within the forearm vascular bed was obtained as measured by a water-filled venous occlusion plethysmograph. The fall in blood pressure was interpreted by the authors as due to a decreased stroke volume dependent on a reduced venous return and to an elimination of the positive inotropic effect on the heart due to the generalized reflex inhibition of sympathetic tone.

RINZLER

Carlsson, A., and Hillarp, N. A.: On the State of the Catechol Amines of the Adrenal Medullary Granules. Acta physiol. scandinav. **44:** 163, 1958.

The granules of the adrenal medulla of the cow which contain the catechol amines were isolated and the amines were resuspended in solutions of varying ionic composition. The catechol amines were found to occur in the granules in an osmotically inactive form; this was shown by analyzing the intragranular fluid. On such analysis, it was found that the granular membrane was permeable to sodium, potassium, and sucrose as well as to the catechol amines.

RINZLER

Maaske, C. A., and Bromberger-Barnea, B.: Excitability of the Normally Beating Heart. Am. J. Physiol. **195:** 575 (Dec.), 1958.

The electrical and mechanical responses to spontaneously beating hearts in situ were studied. Adult dogs were anesthetized and stimulating electrodes were carefully placed upon the right ventricle with a minimum of trauma to the heart. Electrical stimuli were delivered through a time delay circuit triggered by the voltage of the R wave of the electrocardiogram. The stimuli were separated by 20 to 30 heart beats. Threshold values for excitability using square-wave stimuli of 2-millisecond duration were determined at random over the entire cardiac cycle. The plotted excitability curve (strength-interval) was found

t be smooth without any indications of transient
v riations in threshold. Single square wave
s ocks of various durations applied directly to
t e uninjured ventricle were ineffective for the
l oduction of ventricular fibrillation. The use of
c osely adjacent electrodes (3 mm.) limited stim-
u ation to a small and presumably discrete myo-
c rdial area. Excitability recovery for this area
v as synchronous and smooth. In the presence of
r ocardial injury, cardiac excitability was al-
t red by some mechanism and a single shock
c uld cause irreversible muscular incordination or
f rillation.

KAYDEN

Heinberg, H., Gerola, A., and Katz, L. N.: Effect of Hypoxia on Cardiac Oxygen Consumption and Coronary Flow. Am. J. Physiol. **195**: 593 (Dec.), 1958.

Anesthetized open-chest dogs were prepared for total coronary flow measurement. Arterial oxygen content was gradually decreased while cardiac work and myocardial oxygen consumption were measured over a wide range. The percentage of myocardial oxygen content and coronary arteriovenous oxygen difference decreased in proportion to the decline in arterial oxygen. Coronary blood flow increased both when the arteriovenous oxygen decreased and when oxygen consumption increased. Arteriovenous oxygen difference and percentage of oxygen extraction remained fairly constant at each level of arterial oxygen over a wide range of cardiac performance and oxygen consumption. The oxygen cost of cardiac external useful work was not changed during hypoxia. Cardiac effort, the product of blood pressure and heart rate, was only slightly altered by hypoxia. It appears, therefore, that hypoxia is associated with an increase in coronary flow that is adequate to maintain oxygen availability, so that cardiac oxygen consumption occurs at normal oxygen extraction.

KAYDEN

DePaula e Silva, P., Raab, W., and Starcheska, Y. K.: The Dynamic Cycle of the Human Heart during Insulin Hypoglycemia and after Injection of Glucose. Cardiologia **33**: 365, 1958.

The cardiac effects of insulin hypoglycemia have been usually attributed to induced discharges of the adrenal medulla. In order to test whether insulin per se has vagotropic properties the authors administered to 10 normal subjects 50 per cent glucose intravenously followed by insulin at various doses and intervals. Recordings of phonocardiogram and carotid pulse wave were used to determine the length of the various phases of systole. A slight but definite slowing of the heart rate and prolongation of isometric contraction were associated with the injection of hypertonic glucose; this may possibly be explained by the vagotropic action of insulin, whose secretion was believed to be increased during hyperglycemia. Opposite and more intense effects were observed during the insulin-induced hypoglycemia. The potential benefits of the antiadrenergic effects of a glucose infusion during acute left ventricular failure are pointed out.

BRACHFELD

Rowe, G. G., Castillo, C. A., Maxwell, G. M., White, D. H., Jr., Freeman, D. J., and Crumpton, C. W.: The Effect of Mecamylamine on Coronary Flow, Cardiac Work, and Cardiac Efficiency in Normotensive Dogs. J. Lab. & Clin. Med. **52**: 883 (Dec.), 1958.

Several parameters of cardiovascular function were measured before and after the administration of mecamylamine in order to compare the mechanism of action of this agent with other ganglionic blocking agents such as hexamethonium and pentolinium. Experimental subjects were anesthetized supine mongrel dogs. The results were as follows: a significant increase was found in cardiac rate, arterial coronary sinus oxygen difference, and arterial venous oxygen difference, whereas significant decreases occurred in mean arterial blood pressure, mean pulmonary arterial blood pressure, right atrial mean pressure, coronary sinus blood oxygen content, cardiac output, coronary blood flow, and cardiac oxygen consumption. No significant difference was found in total peripheral resistance, but it was noted that the trend was toward an increase. It was concluded that, insofar as the data available were concerned, the actions of mecamylamine were similar to those found with hexamethonium and pentolinium.

MAXWELL

Jacquez, J. A., Poppell, J. W., and Jeltsch, R.: Partial Pressure of Ammonia in Alveolar Aid. Science **129**: 269 (Jan. 30), 1959.

In dogs with portocaval shunts and in normal dogs determinations were made of the ammonia in the alveolar air and in arterial plasma. The partial pressure of ammonia in the alveolar air was found to be the same (within the limits of experimental error) as the calculated partial pressure of ammonia in arterial plasma. These measurements establish that ammonia is present in alveolar air in the order of magnitude expected if the ammonia in the blood were to equilibrate with the alveolar air during its passage through the pulmonary capillaries.

SAGALL

Webb, W. R., and Field, S. E., Jr.: Effect of Anesthetization of A-V Node on Ventricular Fibrillation Following Acute Coronary Arterial Occlusion. Am. J. Physiol. **195:** 403 (Nov.), 1958.

Ligation of the left coronary artery in anesthetized dogs produced ventricular fibrillation in less than 150 seconds. Anesthetization of the atrioventricular (A-V) node with procaine to produce complete atrioventricular dissociation markedly reduced the incidence of ventricular fibrillation. In 14 dogs with idioventricular rhythm after anesthetization, ligation of the left coronary artery caused fibrillation in 3, and the remaining 11 developed bradycardia and standstill after periods up to 45 minutes, without fibrillation or other arrythmia. In 2 dogs with atrioventricular nodal rhythm after procainization, coronary ligation produced ventricular fibrillation at 9 minutes in 1 and the other developed asystole in 11 minutes. Anesthetization of the A-V node may decrease the adrenergic effect of sympathetic fibers that pass through the A-V node.

KAYDEN

PULMONARY DISEASES

Yu, P. N.: Primary Pulmonary Hypertension: Report of Six Cases and Review of Literature. Ann. Int. Med. **49:** 1138 (Nov.), 1958.

Clinical features and laboratory studies in 6 women with primary pulmonary hypertension are presented. Dyspnea and fatigue on exertion were presenting symptoms in all patients. None of the patients had chest pain and 4 of the patients were in right ventricular failure. A loud, split second pulmonic sound was the most striking auscultatory finding. Electrocardiograms showed right axis deviation and varying degrees of right ventricular hypertrophy in all but 1 patient. Fluoroscopy and roentgenograms of the chest showed enlargement of the right ventricle and dilatation of the main pulmonary artery with increased hilar markings and clear peripheral pulmonary vascular shadows. Pulmonary function studies were carried out in 3 patients and revealed a moderate increase in residual volume in 2 patients and a decreased maximal breathing capacity in 1 patient. Hemodynamic data obtained by cardiac catheterization revealed elevation of pulmonary artery pressure in all 6 patients with a mean pressure of 48 to 77 mm. Hg. Pulmonary capillary pressure was recorded in 4 patients and was normal. In the 4 patients with clinical signs of right ventricular failure, there was elevation in the right ventricular end-diastolic and right atrial mean pressures. Five of the 6 patients died within a year of the onset of right ventricular failure. Postmortem examination in 3 patients revealed marked hypertrophy and dilatation of the right ventricle and enlargement of the right atrium. The small pulmonary arteries had marked reduction in their lumina due either to extensive subendothelial proliferation or to slight to moderate hypertrophy of the media. No perivascular inflammatory changes were noted and only 1 patient showed organized thrombi in the small pulmonary arteries. The remainder of this article reviews 55 cases of primary pulmonary hypertension collected from the literaure between 1951 and 1957.

KAYDEN

Fowler, W. D., and Miller, R. D.: Physiologic Considerations in the Diagnosis and Treatment of Ventilatory Insufficiency. Arch. Int. Med. **102:** 866 (Dec.), 1958.

"Ventilatory insufficiency" is a brief expression used to indicate a complex situation that exists when an abnormality in the mechanical aspects of breathing is accompanied by dyspnea at moderate levels of physical activity. There are mechanical devices available to maintain ventilation both in the form of controlled positive and negative pressures. The ventilatory tests, which the authors believe are most widely used, are the measurement of the conventional vital capacity, the rapid or timed vital capacity, and the maximal breathing capacity. An impairment in these tests may be apparent in the early stages of diffuse obstructive emphysema. However, the correlation between these tests and the degrees of dyspnea may be poor. At times the determination of these tests before and after the use of bronchodilating drugs may offer objective evidence of improvement. However, here too, there is lack of good correlation between subjective and objective results.

KRAUSE

Pratt, P. C.: Pulmonary Capillary Proliferation Induced by Oxygen Inhalation. Am. J. Path. **34:** 1033 (Nov.-Dec.), 1958.

The presence or absence of pulmonary capillary proliferation was determined microscopically in 1 group of 10 necropsied patients who had received oxygen therapy during their hospital stay and in a second group of 22 randomly selected necropsy cases. The results indicated that pulmonary capillary congestion and proliferation could be observed even after only 2 days of oxygen therapy in some individuals. Diffuse fibrosis was found to occur in some patients after 1 to 2 weeks of continuous exposure to oxygen. These

pulmonary capillary changes (i.e., congestion, proliferation, fibrosis) were thought to be responsible for the development of oxygen dependence which occurred during and after inhalation of high concentrations of oxygen. The author emphasizes that several obscure pulmonary diseases (i.e., Hamman-Rich syndrome, plasma-cell pneumonia of premature infants, etc.) may be manifestations of oxygen toxicity.

KARPMAN

Capel, L. H., and Smart, J.: Spirometry and Effort Tolerance in Diseases of the Heart and Lungs. Lancet **2**: 771 (Oct.), 1958.

Timed forced expiratory volumes were studied in 500 patients with obstructive airway disease, heart disease or both and in 34 patients with pulmonary fibrosis in order to evaluate the usefulness of this test in assessing the contribution of obstructive airway disease to effort intolerance when heart disease was present. Both the forced vital capacity (FVC) and the 1-second forced expiratory volume (FEV) fell with loss of effort tolerance in each disease. Forced expiratory ratio

$$\left(\text{FER} = \frac{\text{FEV}}{\text{FVC}}\right)$$

fell little in patients with heart disease but fell notably in patients with obstructive airway disease due to a large fall in FEV. The FER may thus distinguish the 2 conditions and point to the major cause of disability. Heart disease and pulmonary fibrosis could not be distinguished by this method.

KURLAND

Bedell, G. N., Wilson, W. R., and Seebohm, P. M.: Pulmonary Function in Obese Persons. J. Clin. Invest. **37**: 1049 (July), 1958.

Twenty-eight extremely obese persons (weighing more than 100 pounds above ideal weight) were studied. Those with normal arterial oxygen saturation had reduced expiratory reserve volumes, reduced maximal breathing capacities, and reduced maximal flow rates. When such patients lost weight, their pulmonary function returned toward normal. Alveolar hypoventilation was found in 10 of 28 patients. Five others had hypoxemia not associated with alveolar hypoventilation. In the author's experience, obese persons with normal lungs, respiratory musculature, and normal respiratory center did not have alveolar hypoventilation. One patient who clinically was a "Pickwickian" patient had normal pulmonary function studies. His somnolence had some cause other than hypoxemia or hypercapnia.

WAIFE

Comroe, J. H.: Causes and Differential Diagnosis of Cyanosis of Cardiopulmonary Origin. Arch. Int. Med. **102**: 862 (Dec.), 1958.

The major function of the lungs is to arteriolize the venous blood. This requires the addition of sufficient oxygen to maintain 97 to 98 per cent saturation of hemoglobin in the arterial blood, the removal of enough carbon dioxide to maintain the arterial carbon dioxide tension at 40 mm. Hg and the arterial pH between 7.39 and 7.41. Arterial anoxemia of cardiopulmonary origin can occur because of inadequate volume of alveolar ventilation, uneven alveolar ventilation in relation to pulmonary capillary blood flow, impairment of alveolar capillary diffusion, the shunting of mixed venous blood around ventilated alveoli, and combinations of these types. The author suggests a plan for the diagnosis of arterial anoxemia of cardiopulmonary origin. First, measure minute ventilation and then calculate the volume of useful, or alveolar ventilation. The rate of respiration times (the depth minus the anatomic dead-space volume) equals the alveolar ventilation. If there is no significant hypoventilation, then perform the oxygen test. If arterial blood oxygen values rise to a maximum, there is no venous arterial shunt and the diagnosis must be either uneven distribution or impaired diffusion or both. Clinical judgment, x-ray studies, and additional pulmonary function tests (carbon dioxide-diffusing capacity, single-breath nitrogen meter test and studies of the mechanical properties of the lungs) can then be used to identify precisely the cause of the anoxemia and suggest proper therapy.

KRAUSE

Soulie, P., and Caramanian, M.: Pulmonary Biopsies during Mitral Commissurotomy. Arch. mal. coeur. **51**: 897 (Oct.), 1958.

Pulmonary biopsies were obtained from 222 patients during commissurotomy for mitral stenosis. These lesions concerned primarily the arterioles, and the intensity and extent of their involvement were parallel to the clinical and radiologic signs. Both the intima and the media usually showed hypertrophy. These changes showed a strict dependence on the pulmonary arteriolar resistance and the arteriolo-capillary pressure gradient, as determined by cardiac catheterization. From the histologic studies alone it was impossible to decide whether muscular spasm or hypertrophy was present. Similarly, only injection technics could show how much of the pulmonary hypertension in mitral stenosis was caused by increased anastomoses between the pulmonary and bronchial arteries.

LEPESCHKIN

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Joekes, A. M., Heptinstall, R. H., and Porter, K. A.: The Nephrotic Syndrome. Quart. J. Med. **27**: 495 (Oct.), 1958.

Twenty-four percutaneous renal biopsies were performed in 20 patients with the nephrotic syndrome. Eight patients had the histologic picture of type 2 nephritis (Ellis) the most constant feature of which was thickening of the basement membrane in the capillary tufts of the glomeruli without prominent tubular changes. Two patients were clinical examples of renal vein thrombosis with diffuse thickening of the basement membrane in all glomeruli and pronounced tubular atrophy. One patient had apparent systematic lupus erythematosus. In none of these patients was there evidence of remission. Three patients showed an appearance similar to benign nephrosclerosis, with scattered hyalinized glomeruli surrounded by collagen. Three were classified as a focal type of glomerulonephritis with endothelial and epithelial cellular proliferation in the tufts, collections of peripheral hyaline in individual lobules and organized crescents. The remaining 3 showed remarkably few changes. Of the latter 9 patients, 4 have had complete remissions; in 1 only a trace of urinary protein persists; in none of the other 4 was there evidence of progression of the renal lesion. It was suggested that a histologic picture other than that usually associated with the nephrotic syndrome is quite common. It was not possible to predict the histologic picture on clinical grounds. Renal biopsy seemed of value for diagnosis, prognosis, and assessment of therapeutic procedures.

KURLAND

Ray, C. T.: Mercurial Diuretics. Arch. Int. Med. **102**: 1016 (Dec.), 1958.

Mercurial diuretics act on the renal tubules. Evidence as to the exact site of action in the tubules favors the proximal tubule. In general, when mercurial diuretics are used, the urine contains more chloride than sodium. This is due to the fact that action of the mercurial is in the proximal tubule where there is inhibition of reabsorption, and sodium and chloride escape into the "uninhibited" distal tubule. Here, removal of sodium through exchange for hydrogen, potassium, and ammonium results in the excess of chloride. In this manner the mercurial diuretic may be primarily natriuretic and yet the urine will contain more chloride than sodium. It has been shown that ammonium chloride administration may potentiate the diuretic effect of mercurials. This effect is due to the increased acidity of body fluids, increased acidity of the urine, and to the increased concentration of chloride in the plasma, so that a greater load of chloride is filtered. Aminophylline given intravenously is said to enhance the diuretic response to mercurials, presumably by increasing the rate of filtration. The outstanding clinical application of the mercurial diuretics is in congestive heart failure, but other forms of edema also respond to this therapy. It is important to be mindful that serious depletion of electrolytes and water may follow their use.

KRAUSE

Baer, D. M., Osborn, J.J., Perkins, H. A., Melrose, D. G., Norman, A., and Gerbode, F.: Serum Electrolyte Observations Following Extracorporeal Circulation. Am. Heart J. **56**: 652 (Nov), 1958.

Experience with 65 patients subjected to open-heart surgery with the aid of extracorporeal circulation, and oxygenation indicated that only minor changes occurred in the serum electrolytes. No significant changes were found in the serum potassium, chloride, or sodium. A slight acidosis and lowering of the carbon dioxide content were encountered, but only rarely was it necessary to correct them. Some postperfusion increase in the blood lactic acid was found, but much of this increase could be accounted for by the accumulation of lactic acid in the blood used to run the pump oxygenator.

SAGALL

Goldsmith, H. J., Cowan, M. A., and Gooder, E.: Familial Outbreak of Acute Glomerulonephritis due to Griffith Type-1 Streptococcus. Lancet **2**: 674 (Sept. 27), 1958.

The incidence of acute nephritis following streptococcal infection varies considerably. In cases of acute nephritis, streptococcal types 4, 12, and 25 have been incriminated whereas other types were only sporadically noted. Four cases of acute glomerulonephritis were reported in 1 family following an upper respiratory infection with *B-hemolytic streptococcus*, Group A, type 1. The organism was recovered from 10 of the 11 members of the family; no other hemolytic streptococcus was found; antibody to type 1 was demonstrated. Of the 10 infected members of family, 3 contracted clinical acute nephritis and a fourth had urinary changes without symptoms. Two of the infected people contracted rheumatic arthritis.

KURLAND

Haddy, F. J., Scott, J., Fleishman, M., and Emanuel, D.: Effect of Change in Renal Venous Pressure upon Renal Vascular Resistance, Urine and Lymph Flow Rates. Am. J. Physiol. 195: 97 (Oct.), 1958.

Measurements of renal function in 1 kidney of dogs during surgery were supplemented by additional measurements in perfused live kidneys with intact nerves, with surgically sectioned hilar nerves, with clinically blocked sympathetic nerves, and with chemically potentiated parasympathetic nerves. Intrarenal resistance as a function of flow rate was increased by elevation of venous pressure. When blood flow rate was held constant, resistance increased as a function of venous pressure only in innervated kidneys and decreased slightly in denervated kidneys. Lymph flow rate increased as a function of venous pressure. Urine flow rate decreased as a function of venous pressure with blood flow rate uncontrolled but did not change when flow rate was constant. Therefore, high renal vein pressures increased resistance by reflex active vasoconstriction as well as by passive vasoconstriction. The reduction in urine flow rate was in part related to these resistance-controlling mechanisms.

KAYDEN

Segar, W. E.: Effect of Hypothermia on Tubular Transport Mechanisms. Am. J. Physiol. 195: 91 (Oct.), 1958.

Plasma and urine concentrations of glucose, phosphorus, amino acid nitrogen, protein, and creatinine were measured in 5 dogs during artificial cooling to 20 C. and during rewarming to 37 C. Changes in urine flow were also studied during the 8 periods of study. A decrease in serum amino acid nitrogen occurred with cooling and was reversed during rewarming. Serum creatinine and protein levels were essentially unchanged. Urine flow increased with cooling and the U/P ratios of phosphorus, amino acid nitrogen, and creatinine decreased. There was minimal increase in protein excretion, but all of the filtered glucose appeared in the urine. It was suggested that 2 transport mechanisms were involved in the reabsorption of amino acids and phosphorus from glomerular filtrate, only 1 of which was affected by cooling. The mechanism responsible for glucose reabsorption was paralyzed by cold.

KAYDEN

Berliner, R. W.: The Regulation of Water Balance and Plasma Sodium Concentration. Arch. Int. Med. 102: 986 (Dec.), 1958.

Sodium and the anions that balance it constitute 90 per cent of the solute of plasma. Furthermore, the concentration of the sodium in plasma reflects the effective osmotic pressure of the body fluids and the state of the body water balance. The kidney is the principal effector of water balance. In this organ reabsorption of water is divided into 3 phases: the proximal tubule, the remainder of the nephron, but the distal convoluted tubule in particular and the collecting tubule and duct. The proximal tubule is freely permeable to water but this is not true of the distal convoluted tubule in the absence of the antidiuretic hormone. It is chiefly because of this property that the antidiuretic hormone prevents the excretion of a dilute urine and it is only a secondary function of the antidiuretic hormone to promote the excretion of a concentrated urine. The release of antidiuretic hormone is normally determined by the effective osmotic pressure of the body fluids. Dilution causes inhibition and concentration naturally causes stimulation of production of the antidiuretic hormone. Water balance is usually precisely controlled, but under stress and in disease states there is a tendency to prevent the rapid excretion of water, which may lead to dilution and hyponatremia. In general, the disorders of water excretion are due to inappropriate secretion of antidiuretic hormone and failure of delivery of adequate amounts of sodium to the diluting segment of the nephron. Pain, nausea, apprehension, certain drugs, trauma, and surgery can act as stimuli for the release of antidiuretic hormone. Diuretics can profoundly alter body electrolytes and fluid balance. The author advises more careful attention to water intake as a method to prevent dilution in severely decompensated cardiac and cirrhotic patients, who are subject to rigid salt restriction.

KRAUSE

Levy, R. I., Weiner, I. M., and Mudge, G. H.: The Effects of Acid-Base Balance on the Diuresis Produced by Organic and Inorganic Mercurials. J. Clin. Invest. 37: 1016 (July), 1958.

It has been known that diuresis produced by organic mercurial compounds is potentiated during metabolic acidosis and suppressed during metabolic alkalosis. The authors studied the role of acid-base balance in this reaction. The effects of varying doses of meralluride and mercuricysteine were compared in normal, acidotic, and alkalotic dogs. It was found that mercuricysteine is a more potent chloruretic and was influenced to a smaller extent by changes in acid-base balance than was meralluride. Dogs receiving hypertonic infusions (which kept chloride concentration and glomerular filtration rate elevated) also received other anions, such as

nitrate, sulfate, and bicarbonate. Under these circumstances, bicarbonate inhibited the mercurial effect, while nitrate and sulfate did not. This finding was interpreted as emphasizing the role of pH in determining mercurial effectiveness. Since there was an almost identical chloride load, it is suggested that diuretic activity results from the rupture of a carbon-to-mercury bond with the liberation of mercuric ions.

WAIFE

ROENTGENOLOGY

Doerr, W. and Koch, H.: On a Disturbance in the Texture of the Walls of the Pulmonary Veins in a Case of Turner's Syndrome (Lethal Pulmonary Hemorrhage after Aortography). Arch. Kreislaufforsch **29**: 1 (Sept.), 1958.

A 31-year-old woman showing the Morgagni-Turner-Albright syndrome (agenesis of ovaries, pterygium colli, kyphoscoliosis) and having a masculine nuclear chromatin pattern was submitted to aortography for the purpose of localization of an isthmic aortic stenosis. A few hours after aortography was performed through the right brachial artery, pulmonary hemorrhage set in, and the patient died in pulmonary edema after 2½ days. At autopsy the hemorrhage was found to originate in numerous venous ectasies and varices in the left lower lobe; the wall of the venules showed mucoid-hyaline swelling. These changes, together with the extreme necrosis of the aortic media accompanied by destruction of elastic fibers, were attributed to a congenital metabolic defect of the connective tissues. The rupture of pulmonary veins leading to hemorrhage was attributed to an increase in the already elevated pulmonary venous pressure in connection with the aortography.

LEPESCHKIN

Wylie, E. J., Goldman, L.: The Role of Aortography in the Determination of Operability in Arteriosclerosis of the Lower Extremities. Am. Surg. **148**: 325 (Sept.), 1958.

The experience obtained in the performance of translumbar aortography in 500 patients with arteriosclerotic obstructive lesions involving the abdominal aorta and its distal branches to the level of the popliteal artery was reviewed. It was found that aortography added important surgically significant information to that determined solely by clinical examination. The practical value of this information was manifested in the final determination of operability and in the selection of the site and method of operation.

SAGALL

Coddon, D. R., and Krieger, H. P.: Circumstances Surrounding Complications of Cerebral Angiography. Analysis of 546 Consecutive Cerebral Angiograms. Am. J. Med. **25**: 580 (Oct.), 1958.

The circumstances that surrounded the occurrence of 109 complications in 86 of 546 patients subjected to angiography were analyzed. All patients had been tested with Diodrast prior to the injection of 10 to 12 ml. of a 35-per cent solution, but 6 allergic reactions occurred. Forty-four complications were innocuous and transient; 51 were serious but transient; 14 were permanent. Eight deaths occurred, only 1 of which appeared to be directly related to arteriography. The rate of complications in patients with depressed consciousness was 56 per cent, about 3 times that in the fully conscious group. Eighty-seven per cent of the deaths and 67 per cent of the serious complications occurred in patients whose neurologic state showed rapidly progressive deterioration. No relation was noted to the number of injections of contrast medium, vascular status, or age of the patient. The incidence of complications was almost 3 times greater in patients receiving intravenous amobarbital or pentobarbital than in those receiving only local anesthesia following premedication with intravenous atropine and phenobarbital. Neither fresh blood in the spinal fluid, intracranial aneurysm, nor intracranial hematomas were regarded as contraindications to arteriography, although one fourth of the patients with aneurysm suffered a serious complication. The hazards of arteriography must be weighed against the diagnostically useful information obtained in 80 per cent of these cases.

KURLAND

Anlyan, W. G., Baylin, G. J., Fabrikant, J. L., and Trumbo, R. B.: Studies in Coronary Angiography. Surgery **45**: 8 (Jan.), 1959.

This report describes a systematic evaluation of the many variables in coronary angiography on dogs. Control and repeat angiograms were obtained following production of myocardial infarction by ligation of the left anterior descending coronary artery. Consistent adequate visualization of the coronary tree was obtained by the injection of 30 ml. of 50 per cent Hypaque with an automatic injector through an intra-arterial catheter with the tip located at the junction of the brachiocephalic artery and the ascending aorta. Temporary cardiac arrest of 5 to 15 seconds with intravenous administration of 4 to 8 mg. of acetylcholine markedly improved and simplified the technic without detrimental effects.

No additional hazard with coronary arteriography with or without the use of acetylcholine) was found in the dogs with myocardial infarcts.

SAGALL

Richards, L. S. and Thal, A. P. Phasic Dye Injection Control System for Coronary Arteriography in the Human. Surg., Gynec. & Obst. **107**: 739 (Dec.), 1958.

A device for timed rapid injection of radiopaque media has been found to be effective and safe in producing coronary arteriograms in man and animals. It consisted of an electronic control system, triggered by the R wave of the electrocardiogram, and a compressed nitrogen-driven syringe. The latter was connected to a large bore polyethylene catheter inserted through the brachial artery to a point 1 cm. above the aortic valve. Usually, 30 to 50 ml. of 90 per cent diatrizoic acid (Hypaque) was delivered under 150 pounds per square inch pressure in 0.6 to 1.0 second. Coronary arteriograms of excellent quality showing secondary and tertiary branches have been regularly obtained both in healthy and diseased coronary circulation.

ROGERS

SURGERY AND CARDIOVASCULAR DISEASE

Perkins, H. A., Osborn, J. J., and Gerbode, F.: The Effect of Heparin on the Platelet Count in Vitro, with Particular Reference to the Collection of Blood for Extracorporeal Circulation. Am. J. Clin. Path. **30**: 397 (Nov.), 1958.

Blood was collected from human donors into different containers with varying amounts of heparin. Platelet counts were performed at various times after collection. Platelet survival in blood collected into plastic bags containing a small quantity of acidified citrate-dextrose solution and 2,000 units of heparin was excellent for four hours. Clumping of platelets occurred after 24 hours in this solution, and at 11 days there was a definite reduction in the number of platelets. Platelet survival in blood drawn directly into empty plastic bags was somewhat reduced after 4 hours. Blood drawn into siliconed glass bottles containing 1,800 units of heparin in a glucose-saline menstruum had almost the same platelet count at the end of 4 hours as control specimens. Observations of platelet survival in small counting vials indicated that the greatest fall in the number of platelets occurred in the first few minutes of incubation at room temperature and that the fall in platelet count was greater when the concentration of heparin was less. There was little difference in platelet survival in blood drawn into uncoated glass containers, into siliconed glass bottles or polyethylene bags in these studies. The least loss in platelet counts occurred when the volume of blood was large enough almost entirely to fill the container.

KAYDEN

Thomas, J. A., Vaysse, J., d'Allaines, C., Laurent, D., Chevrier, J. L., Ricordeau, G., Jaulmes, B., du Bouchet, N., Mirabel, J., Latscha, B. I., Arfel, G., Vallon, M., and d'Allaines, J.: The Heart-Lung Machine with an Artificial Pulmonary Membrane. First Surgical Results. Arch. mal. coeur. **51**: 801 (Sept.), 1958.

The machine consists of a rotating cylinder covered with a thin plastic fabric-supported film, and filled on the inside with a constantly renewed aerosol of oxygen in buffered saline solution. The cylinder is partly immersed in the blood reservoir. Condensation of the saline on the plastic film provides complete separation between oxygen and blood and prevents formation of microscopic bubbles. Only plastic surfaces are in contact with the blood. A double multi-cuspid plastic diaphragm pump provides an output up to 5 L./min. and does not cause hemolysis of more than 6 mg. of hemoglobin per hour. The apparatus is provided with an electric output meter and with a thermostatically controlled heater. Seven patients with atrial septal defects were operated upon satisfactorily with this apparatus; in 5 of these Ivalon plastic prostheses were inserted. In 1 patient excessive hemolysis was caused by too intense infra-red radiation, while another patient, who had previously shown pulmonary edema and in whom the operation lasted exceptionally long, died 3 days later with symptoms of decerebration and hemolytic anuria.

LEPESCHKIN

VASCULAR DISEASE

Björkman, S. E.: Phenylbutazone in the Treatment of Temporal Arteritis. Lancet **2**: 935 (Nov.), 1958.

Phenylbutazone was utilized to treat 8 patients with temporal arteritis whose diagnosis was verified by biopsy or postmortem examination in 5 instances. In the other cases, diagnosis was made on clinical grounds. Pain and fever were invariably controlled as rapidly as when steroids were used. General condition improved. Neither side effects nor relapses were seen but sedimentation rate was not influenced. The relief was thought to be due, at least in part, to regression of concomitant thrombophlebitis of the temporal vein.

KURLAND

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N.Y.

Telephone Gramercy 7-9170

AHA TO BE PUBLISHER OF ITS TWO JOURNALS

Effective January 1, 1960, the American Heart Association will begin direct publication of its two official professional journals, *Circulation* and *Circulation Research*, it has been announced by J. Scott Butterworth, M.D., Chairman of the AHA Publications Committee.

Mr. Alan Baird Hastings, formerly of Harvard University Press, has been named by the Association as Publishing Director for both journals. Publication office will be the American Heart Association, 44 East 23rd Street, New York 10, N.Y. As in the past, all communications on editorial matters should be directed to the editors of *Circulation* and *Circulation Research*.

AHA SCIENTIFIC SESSIONS

The six sessions of broad clinical interest to be held during the American Heart Association's 32nd annual Scientific Sessions in Philadelphia, October 23-25, have been classified by the American Academy of General Practice as acceptable for Category II credit for Academy members. Under sponsorship of the Association's Council on Clinical Cardiology, these clinical sessions will run concurrently with special scientific sessions and programs sponsored by other Councils of the Association at which original investigative work will be reported.

The program this year will also include a joint session with the American College of Cardiology which is conducting its Interim Meeting to coincide with the AHA Scientific Sessions. The College has scheduled on Friday evening, October 23, its popular "Fireside Conferences" in which Heart Association members will participate. On Sunday afternoon, October 25, the College will present a panel jointly with the Council on Clinical Cardiology on the subject of "Cardiac Resuscitation."

In addition, the Association's Council on Arteriosclerosis, formerly the American Society for the Study of Arteriosclerosis, will participate in a panel on "Conflicting Concepts of Atherogenesis" on Sunday morning and also in an afternoon program on arteriosclerosis. The Council on Arteriosclerosis will hold its business and independent scientific meetings in Chicago, November 8-9, 1959.

Secretary Arthur S. Flemming of the U.S. Department of Health, Education, and Welfare, will be guest speaker at a business luncheon of the Council on Community Service and Education on Saturday, October 24 at the Bellevue-Stratford Hotel. Mr. Flemming will speak on "The Role of Voluntary Health Associations in Meeting Future Health Needs."

Following is an outline of the Scientific Sessions program:

Friday, October 23:

Morning: Session on clinical cardiology devoted to a symposium on "Cardiovascular Regulation and Its Role in Cardiovascular Disease"; simultaneous sessions on rheumatic fever and congenital heart disease, and on circulation.

Afternoon: Presentation of submitted papers of general interest in clinical cardiology; Lewis A. Conner Memorial Lecture, "The Performance of the Heart," by Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago; session on cardiovascular surgery.

Saturday, October 24:

Morning: Session on clinical cardiology consisting of two symposia: "Recent De-

velopments in Diagnostic Techniques" and "Open Heart Surgery in Acquired Valvular Heart Disease"; simultaneous session on high blood pressure research.

Afternoon: Presentation of the Association's Albert Lasker Award; George E. Brown Memorial Lecture, "Circulatory Congestion and Heart Failure," by Ludwig W. Eichna, M.D., Professor of Medicine, New York University College of Medicine; symposium on "Congestive Heart Failure," including a panel, "Treatment of Congestive Heart Failure," and a presentation "A Useful Life After Heart Failure"; session on basic science; session on cardiovascular surgery.

Sunday, October 25:

Morning: Panel on "Conflicting Concepts of Atherogenesis"; concurrent session on "Instrumental Methods in Cardiovascular Research."

Afternoon: Joint panel with the American College of Cardiology on "Cardiac Resuscitation"; session on arteriosclerosis.

The Scientific Sessions program will also include a session on medical motion pictures. Each film will be introduced by the author and will be followed by discussion. A section of scientific and industrial exhibits will also be included. The Heart Association's Annual Dinner will be held on Sunday evening.

AHA ANNUAL MEETING

Following the Scientific Sessions, the 35th Annual Meeting of the Assembly, delegate body of the Association, will be held on October 26-27 at the Bellevue-Stratford Hotel. Six Assembly Panels, in session all day Monday, will discuss: Research; Fund Raising; Relationships and Responsibilities Between National, State and Local Heart Associations; Community Relationships of Heart Associations; Program Activities in Community Service and Education; and Heart Association Organization.

The general session of the Assembly meets on Tuesday morning to review panel recommendations and elect officers and Board members of the Association.

DEADLINE IS SEPTEMBER 15 FOR AHA FELLOWSHIP APPLICATIONS

September 15, 1959, is the deadline for submitting applications for Research Fellowships and Established Investigatorships to be awarded by the Association for the fiscal year beginning July 1, 1960. Applications for Grants-in-Aid must be received by November 1, 1959.

All applications must be made on forms available from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y. Stipends for *Established Investigators* range from $6,500 to $8,500, plus departmental allowances; for *Advanced Research Fellowships,* $4,600 to $6,500, plus a $500 departmental allowance; and for *Research Fellowships,* from $3,800 to $5,700.

AFFILIATES PROVIDE $24,300 FOR NATIONAL RESEARCH PROGRAM

The Illinois Heart Association has provided $15,500 and the New Jersey Heart Association $8,800 to be applied to the AHA national research support program. These contributions were made in response to requests from the Association's National Office for supplementary research support from affiliates and chapters to help reduce a deficit in the national grants-in-aid budget. Such additional aid will help underwrite a record total of approximately $3,300,000 awarded for the 1959-60 fiscal year.

Supplementary funds to the national research program, which are in addition to amounts regularly assigned by Heart Associations for national research, last year totaled $106,895 from 10 affiliates and 13 chapters.

The sum from Illinois will be applied to support in full the Established Investigatorships of Ruth Pick, Medical Research Institute, Michael Reese Hospital, and Victor E.

Pollak, University of Illinois College of Medicine, both in Chicago. The New Jersey Contribution is in full support of the grant of Milton Helpern, New York University Postgraduate Medical School.

NEW AHA BOOKLET ISSUED ON HOME CARE OF RF CHILD

A new booklet, "Home Care of the Child with Rheumatic Fever," prepared to give practical assistance to mothers confronted with the many problems of caring for such children, has been published by the American Heart Association. Physicians may obtain copies for distribution to families of their rheumatic fever patients from local Heart Associations or from the American Heart Association.

The illustrated publication emphasizes the importance of close cooperation between the physician and members of the family, particularly in safeguarding against recurrent attacks. Specific suggestions are listed for adding to the patient's comfort through the use of standard and improvised equipment. In addition to a planned schedule which would ease the burden of patient and parent, the booklet presents suggestions for a well-balanced diet. A number of sources are listed for obtaining further information on home nursing care, emotional aspects of illness in children, and nutritious diets.

The booklet points out that many Heart Associations will arrange film showings and talks by physicians for groups of interested parents on the subject of rheumatic fever.

HEART BULLETIN CONTAINS EXERCISE TEST MATERIALS

A symposium and several articles of special interest and use to the practicing physician in cardiovascular disease on the subject of "Exercise Tests in Patients" are contained in the July-August issue of *The Heart Bulletin*. The publication, sponsored by the American Heart Association in cooperation with the National Heart Institute and the American Academy of General Practice, is distributed as a service to practicing physicians by many local Heart Associations.

Included in the July-August issue are *A Symposium: The Two-Step Exercise Test*, by Arthur M. Master, M.D., and Ephraim Donoso, M.D.; *Value of the Postexercise Electrocardiographic Test*, by Thomas W. Mattingly, M.D.; *The Master Exercise Test in Patients with Coronary Heart Disease and Normal Subjects*, by Robert E. Mason, M.D.; *Stress and the Heart*, by William Dock, M.D.; *Pheochromocytoma: Evaluation of Pharmacologic and Chemical Tests as an Aid to Diagnosis*, by Grace M. Roth, Ph.D., Eunice V. Flock, Ph.D., and Walter F. Kvale, M.D.; and *Transposition of the Great Vessels*, by Robert A. Miller, M.D.

The Heart Association has appointed seven Associate Medical Editors for the *Bulletin* which was initiated in 1952 as a public service by the Medical Arts Publishing Foundation, Houston.

AHA SLIDE KIT AVAILABLE FOR PHYSICIAN SPEAKERS

As an aid to physician speakers, a Resource Slide Kit consisting of 188 Kodachrome and black and white slides on the subject of heart and circulatory diseases has been compiled by the American Heart Association. The complete set, including a small lighted viewer for selecting slides, is available from the Association's National Office, 44 East 23rd Street, New York 10, N.Y., for $60, a price made possible by mass duplication.

A table of contents and descriptive material accompany the slides, which are grouped for medical and for combined medical and lay audiences. Included in the set for medical audiences are electrocardiograms, heart drawings and heart models and cardiac silhouettes. Further information regarding the subject matter for combined medical and lay audiences may be obtained from the Association.

Mounted on standard 2 x 2 inch cardboard, the 35 mm. slides come in a metal box designed to hold 300 cardboard mounted slides, thus allowing the user to add his own or additional AHA slides as they become available.

OFFER ARTHRITIS STUDY AWARDS

Predoctoral, postdoctoral and senior investigatorship awards in the fundamental sciences related to arthritis are being offered by the Arthritis and Rheumatism Foundation for work beginning July 1, 1960. Deadline for applications is October 31, 1959. Further information and application forms may be obtained from the Foundation's Medical Director, 10 Columbus Circle, New York 19, N. Y.

ANGIOLOGY SOCIETY RENAMED

The International Society of Angiology announced that it has been renamed The International Cardiovascular Society, with new offices at 715 Park Avenue, New York 21, N. Y. Michael E. De Bakey, M.D., Houston, is President and Henry Haimovici, M.D., New York, Secretary-General.

MEETINGS CALENDAR

September 13-17: International College of Surgeons, U.S. Section, Chicago. Ross T. McIntire, 1516 Lake Shore Drive, Chicago 10, Ill.

September 22-25: American Roentgen Ray Society, Cincinnati. C. A. Good, 200 First Street, S.W., Rochester, Minn.

September 28-October 2: American College of Surgeons, Atlantic City. Paul R. Hawley, 40 E. Erie Street, Chicago 11, Ill.

October 14-17: American College of Chest Physicians, Albuquerque, N. Mex. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

November 2-4: Association of American Medical Colleges, Chicago. Ward Darley, 2530 Ridge Avenue, Evanston, Ill.

November 6-7: Central Society for Clinical Research, Chicago. A. S. Weisberger, 2065 Adelbert Road, Cleveland 6, Ohio.

November 8-9: American Heart Association's Council on Arteriosclerosis, Chicago. Aaron Kellner, N. Y. Hospital, 525 E. 68th Street, New York 21, N. Y.

November 10-12: Conference on Electrical Techniques in Medicine and Biology, Philadelphia. Herman P. Schwan, University of Pennsylvania, Philadelphia, Pa.

1960

February 3-6: American College of Radiology, New Orleans. William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

February 18-20: Central Surgical Association, Chicago. Angus D. McLachlin, Victoria Hospital, London, Ontario, Canada.

ABROAD

September 18-20: International Cardiovascular Society, Munich, Germany. H. Haimovici, 715 Park Avenue, New York 21, N. Y.

September 20-26: Mexican National Institute of Cardiology, International Symposium and Congress, Mexico City. Manuel G. Noguera, National Institute of Cardiology, Av. Cuauhtemoc 300, Mexico, D.F.

1960

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Avenue, New York 22, N. Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmasse, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

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